528 Rec'd PCT/PTO 26 DEC 2000

FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
200936USPCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
09/719554

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR99/01513	**23 JUNE 1999**	**23 JUNE 1998**

TITLE OF INVENTION
NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY WITH HUMAN ENDOGENOUS RETROVIRAL MOTIFS, AND THEIR USES

APPLICANT(S) FOR DO/EO/US
Patric M. ALLIEL, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Notice of Piority
PCT/IB/304
PCT/IB/308
Drawings (64 Sheets)
Sequence Listing (84 Sheets)

PCTUS1/REV03

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U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/719554	PCT/FR99/01513	200936US0PCT

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

CALCULATIONS PTO USE ONLY

☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00**

☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$860.00**

☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).	☐ 20	☒ 30		**$130.00**	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	37 - 20 =	17	x $18.00	**$306.00**	
Independent claims	6 - 3 =	3	x $80.00	**$240.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,536.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☐	**$0.00**	
SUBTOTAL =				**$1,536.00**	
Processing fee of **$130.00** for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)).	☐ 20	☐ 30	+	**$0.00**	
TOTAL NATIONAL FEE =				**$1,536.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
TOTAL FEES ENCLOSED =				**$1,536.00**	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$1,536.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Surinder Sachar
Registration No. 34,423

Surinder Sachar

SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER

Dec. 26 2000

DATE

#4

200936USOPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
PATRICK ALLIEL ET AL	: ATTN: APPLICATION DIVISION
SERIAL NO: 09/719,554	:
FILED: December 26, 2000	:
FOR: NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY WITH HUMAN ENDOGENOUS RETROVIRAL MOTIFS, AND THEIR USES	:

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Communication mailed April 30, 2001, Applicants submit herewith a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. Prior to examination on the merits, please amend the above-identified application as follows.

IN THE SPECIFICATION

Please amend the specification as follows:

Page 69 (Abstract), after the last line, beginning on a new page, please delete the original Sequence Listing and replace with the substitute Sequence Listing appended herewith.

<u>REMARKS</u>

Claims 1-37 are active in the present application. Applicants have now submitted a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. The sequence information recorded in the corresponding computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing. Support for all of the sequences listed in the substitute Sequence Listing is found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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09/719554
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200936US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

PATRICK M. ALLIEL ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW PCT APPLICATION :
(Based on PCT/FR00/01513)

FILED: HEREWITH :

FOR: NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY WITH HUMAN ENDOGENOUS RETROVIRAL MOTIFS, AND THEIR USES :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend the claims as follows:

3. (Amended) A nucleic acid fragment, characterized in that it comprises a segment of a sequence as claimed in claim 1 [or claim 2] and in particular the sequence SEQ ID NO: 3-22, 28 and 61, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences as well as fragments derived from the coding

regions of the preceding sequences corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

4. (Amended) Transcripts, characterized in that they are generated from the sequences as claimed in [any one of claims 1 to 3] claim 1.

5. (Amended) A diagnostic reagent for the differential detection if complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label.

10. (Amended) A method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the *env* or *env* and *gag* type, their normal or pathological variants, by hybridization and/or gene amplification, carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analyzed is brought into contact with at least one probe as claimed in claim 5[, claim 6 or claim 8,] and

(b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

11. (Amended) The method of detection as claimed in claim 10, characterized in that it comprises:

- prior to step (a):

- a step of preparing the relevant biological tissue or fluid,

- a step of extracting the nucleic acid to be detected, and

- at least one gene amplification cycle carried out with the aid of at least one reagent [as claimed in any one of claims 5 to 7] selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label, and subsequent to step (b):

- a step of comparing the nucleic sequences obtained in the said biological sample with the human endogenous retroviral sequences SEQ ID NO: 1 or SEQ ID NO:2 or to a sequence exhibiting a level of homology with SEQ ID NO: 1 or SEQ ID NO:2 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains [as claimed in any one of claims 1 to 3], by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a deletion or a single mutation between the various sequences compared.

12. (Amended) A method of detecting the transcripts as claimed in claim 4, characterized in that it comprises:

- collecting messenger RNAs obtained from control biological samples and from a similar sample collected from patients, and

- the qualitative and/or quantitative analysis of the said mRNAs by *in situ* hybridization, by dot-blot, Northern blotting, RNAse mapping or RT-PCR, with the aid of a diagnostic reagent selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label [as claimed in any one of claims 5 to 9].

13. (Amended) Chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence selected from the group consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, associated with an endogenous retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides as claimed in [claims 1 to 4] claim 1.

14. (Amended) A method for the detection and/or evaluation of an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, wherein the sequence are SEQ ID NO: 1 or SEQ ID NO:2 or

to a sequence exhibiting a level of homology with SEQ ID NO: 1 or SEQ ID NO:2 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains [as claimed in any one of claims 1 to 9], characterized in that it comprises:

- depositing on an appropriate support, cDNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or from specific oligonucleotide sequences, the said DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/ deregulation of motifs belonging to the said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as claimed in claim 13,

- the hybridization of the said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and

- the detection of the hybrids formed.

16. (Amended) The method as claimed in claim 14 [or claim 15], characterized in that the said support comprises, in addition, any endogenous or exogenous retroviral sequence.

17. (Amended) The kit for the detection and/or evaluation of an autoimmune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in addition to the buffers necessary for carrying out a method according to [any one of claims 14 to 16] <u>claim 14</u>:

- diagnostic reagents A <u>selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label</u> [as claimed in any one of claims 5 to 9], and

- reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

19. (Amended) Translational products, characterized in that they are encoded by a nucleotide sequence as claimed in [any one of claims 1 to 4] claim 1.

20. (Amended) A peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO: 1-22, 28 and 61 as claimed in [any one of claims 1 to 4] claim 1.

22. (Amended) The peptide as claimed in claim 20 [or claim 21], characterized in that it is selected from the group consisting of:

- the sequences SEQ ID NO: 23-36;

- the sequence SEQ ID NO: 58;

- a C-terminal fragment of the sequence SEQ ID NO: 26, either from the amino acid 291, or from the amino acid 321, starting from the first methionine of the sequence SEQ ID NO: 26;

- a peptide of the CKS-17/CKS-25 type present in one of the sequences SEQ ID NO: 23-36 or 58; and

- the peptides having affinity with one of the haplotypes of the class I or class II HLA system and in particular the fragments 399-471, 244-271 of enverin, as well as the peptides having the sequence SEQ ID NO: 68-118, in accordance with Table I.

23. (Amended) The peptide as claimed in [any one of claims 20 to 22] claim 20, characterized in that it is obtained from nucleic sequences as claimed in any one of claims 1 to 4, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).

26. (Amended) The composition as claimed in claim 24 [or claim 25], characterized in that said peptide has the sequence SEQ ID NO: 120.

27. (Amended) An antibody, characterized in that it is directed against one or more of the peptides as claimed in [any one of claims 20 to 23] claim 20.

30. (Amended) A method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences as claimed in [any one of claims 19 to 23] claim 19.

31. (Amended) An application of the sequences as claimed in [any one of claims 1 to 9, 13, 14 or 19 to 23] claim 1 to the diagnosis of, to the prognosis of, to the evaluation of genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part of the sequences [as claimed in to any one of claims 1 to 5] in claim 1 and related endogenous or exogenous forms are involved.

32. (Amended) Hybrid nucleic sequences, characterized in that they comprise sequences or motifs as claimed in [any one of claims 1 to 9] claim 1, combined with sequences or motifs of endogenous origin or of exogenous origin or induced exogenously.

33. (Amended) A recombinant cloning or expression vector, characterized in that it comprises a nucleic sequence as claimed in [any one of claims 1 to 4] claim 1.

35. (Amended) A gene therapy vector, characterized in that it comprises all or part of the endogenous retroviral nucleic sequences of the HERV- 7q type as claimed in [any one of claims 1 to 4] claim 1.--

REMARKS

Claims 1-37 are active in the present application. The claims are amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

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NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY WITH HUMAN ENDOGENOUS RETROVIRAL MOTIFS, AND THEIR USES

The present invention relates to a novel nucleic sequence and deduced protein sequence family with complete or partial human endogenous retroviral motifs, and sequences flanking or adjacent to said sequences, and controlled by the latter; modification of the expression or impairment of the structure (polyadenylation, alternative splicing and the like) of said flanking sequences.

The invention also relates to the detection and/or use of said nucleic sequences and of said corresponding protein sequences in the context of diagnostic, prophylactic and therapeutic applications, in particular for neuropathological conditions with an autoimmune component such as multiple sclerosis.

The invention also relates to the production of antisense double-stranded and single-stranded nucleic probes, of ribozymes, capable of modulating viral replication (T.R. Cech, Science, 1987, **236**, 1532-1539; R.H. Symons, *Trends Biochem. Sci.*, 1989, **14**, 445-450) of the corresponding recombinant molecules, and associated antibodies.

Retroviruses are viruses which replicate solely by using the opposite route to the conventional processing of genetic information. This process, called reverse transcription, is mediated by an RNA dependent DNA polymerase or reverse transcriptase, encoded by the *pol* gene. Retroviruses also encode at least two additional genes. The *gag* gene encodes the proteins of the skeleton, matrix, nucleocapsid and capsid. The *env* gene encodes the envelope glycoproteins. Retroviral transcription is regulated by promoter regions or "*enhancers*" situated in highly repeated regions or LTR (*Long Terminal Repeat*) and which are present at both ends of the retroviral genome.

During the infection of a cell, polymerase makes a DNA copy of the RNA genome; this copy may then

integrate into the human genome. Retroviruses do not kill the cells which they infect, but on the contrary often enhance their rate of growth. Retroviruses can infect germ cells or embryos at an early stage; they can, under these conditions, integrate the germ line and be transmitted by vertical Mendelian transmission, which constitutes the closest relationship between a host and its parasite. These endogenous viruses can degenerate during generations of the host organism and lose their initial properties. However, some of them may conserve all or part of their properties or of the properties of their constituent motifs, or acquire novel functional properties having an advantage for the host organism, which would explain the preservation of their sequence.

The existence of endogenous motifs having long open reading frames and/or subjected to a strong selection pressure can therefore be an indication of a preserved or acquired biological function, which may correspond to a benefit for the host organism. These retroviral sequences can also undergo, over the generations, discrete modifications which will be able to trigger some of their potentials and generate or promote pathological processes. It has recently appeared necessary to carry out a review and to identify these sequences so as to be able to evaluate their functional impact.

Human endogenous retroviral sequences or HERVs represent a substantial part of the human genome. These retroviral regions exist in several forms:

- complete endogenous retroviral structures combining *gag, pol* and *env* motifs, flanked by repeat nucleic sequences which exhibit a significant analogy with the LTR-*gag*-*pol*-*env*-LTR structure of infectious retroviruses,

- truncated retroviral sequences; for example the retrotransposons lack their *env* domain and the retroposons do not possess the *env* and LTR regions.

Up until now, the study of these regions of the genome has been neglected in humans for essentially two reasons:

- the existence of insertions/deletions which can shift the reading frame and of mutations which modify the sequence. These modifications cause impairment of the structure and consequently of the biological function of these motifs,

- the absence of confirmed associations with human pathological conditions.

The recent knowledge of fragments which are significantly representative of the human genome and an orientation of research studies toward a study of structure/function of endogenous retroviral motifs have made it possible to specify the importance of these regions. The involvement of truncated or complete endogenous sequences in pathological conditions in animals is documented; for example their association with tumor processes has been clearly demonstrated (S.K. Chattopadhyay et al., 1982, Nature, **295**, 25-31). Research aimed at specifying the association or the influence of HERVs in human pathological conditions is now therefore justified.

A classification of the HERV elements has been proposed (Tönjes R.R. et al., *AIDS & Hum. Retroviral.*, 1996, **13**, p261-p267; A.M. Krieg et al., FASEB J., 1992, **6**, 2537-2544). It is based on a homology of these sequences with retroviruses isolated in animals, with the aid of heterologous retroviral probes. Indeed, in general, the HERVs exhibit relatively little homology with known human infectious retroviruses.

The class I families exhibit a sequence homology with the type C mammalian retroviruses; there may be mentioned in particular the ERI superfamily, close to the MuLV virus (*murine leukemia virus*) and to the BaEV virus (*baboon endogenous virus*).

The class II families exhibit a sequence homology with the type B mammalian retroviruses such as

MMTV (*mouse mammary tumor virus*) or the type D retroviruses such as SRV (*squirrel monkey retrovirus*).

Other families have also been described; among these, there may be mentioned HERVs which exceptionally exhibit partial homology with HTLV-1 (RTVL-H) or primate viruses; HRES-1, for example, exhibits sequence homology with HTLVs.

Programmes for very large sequencing of the human genome now make it possible to have available a significant number of novel retroviral sequences. The use of data processing software packages makes it possible to identify and analyse these genes. In this context, a systematic search relating to the entire information available to date has been initiated in order to identify novel human endogenous retroviral sequences as a function of certain analytical criteria:

- presence of long open reading frames conserved during evolution of the host organism and which may suggest a biological function,
- analogy with sequences already characterized outside or inside the retrovirus domain,
- location in regions of susceptibility for certain pathological conditions or close to essential genes, for example in the cancer domain, regulation of the immune system or in certain neuropathological conditions.

The work carried out by the inventors on sequence databases allowed them to identify a set of endogenous retroviral sequences or motifs whose normal or pathological expression can promote or disrupt a protective effect in relation to pathological processes, or play a role in the onset or worsening of pathological conditions.

The subject of the present invention is a purified nucleic acid fragment, characterized in that it comprises all or part of a sequence encoding a human endogenous retroviral sequence, which has at least *env*-type retroviral motifs, corresponding to the sequence SEQ ID NO: 1 or to a sequence exhibiting a level of

homology with said sequence SEQ ID NO: 1 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains.

The expression homologous sequence is understood to mean both a sequence which exhibits complete or partial identity with the abovementioned sequence SEQ ID NO: 1 and a sequence which exhibits partial similarity with said sequence SEQ ID NO: 1.

According to an advantageous embodiment of said fragment, it has retroviral motifs corresponding to an *env* domain and corresponding to the sequence SEQ ID NO: 1 and retroviral motifs corresponding to a *gag* domain and corresponding to the sequence SEQ ID NO: 2 or to a sequence exhibiting a level of homology greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains and a level of homology greater than or equal to 90% on more than 700 nucleotides or greater than or equal to 70% on more than 1 200 nucleotides for the *gag*-type domains, said motifs having no insertion or deletion of more than 200 nucleotides.

Said fragments constitute a novel family of human endogenous retroviral sequences (HERV-7q family) which exhibits sequence homology with the MSRV retroviruses, as described in International Application WO 97/06260; said fragments according to the present invention have:

- two repeat nucleotide motifs of 711 bp (Figure 3), having characteristic signals identified in LTRs (*Long Terminal Repeats*): transcription promoters of the TATAA or CCAAT box type. These repeat domains delimit three deduced motifs of the *gag, pol* and *env* type (Figure 2),

- an *env*-type motif (positions 6965 nt - 9550 nt on the sequence SEQ ID NO: 3 or in Figure 1) which contains a long open reading frame of 1 620 nucleotides (positions 7874-9493 of the sequence

ID NO: 3 and Figure 1) encoding a protein having an unpublished sequence of 540 amino acids called enverin (Figure 4 and SEQ ID NO: 26) and underlined fragment in Figure 18. There is present inside the transmembrane domain of this *env* domain a peptide motif of the CKS-25/CKS-17 type (Figure 5), recognized as having immunosuppressive functions on the host lymphocytic cells (M. Mitani et al., 1987, *Proc. Natl. Acad. Sci.* USA, **84**, 237-240). A *zinc finger* type domain $\mathbf{HX_{3-4}HX_{22-33}CX_2C}$ (Kulkolski et al., 1992, *Mol. Cell. Biol.*, **12**, 2331-2338), which is present in integrase-type domains is identified in another reading frame. This particular *env* domain signatures the characteristic of novel endogenous retroviral motifs,

the motif (positions 3065 nt - 4390 nt on the sequence SEQ ID NO: 3) of the *gag* type encoding protein motifs according to Figure 6 (SEQ ID NO: 58) (positions 3118-4198 of SEQ ID NO: 3) was identified by virtue of analogies with known *gag* domains. The region of major homology $\mathbf{QX_3EX_7R}$ is for example present (Benit et al., 1997, *J. Virol.*, **71**, 5652-5657). The nucleic acid binding motif $\mathbf{CX_2CX_{3-4}HX_4C}$, situated at the C-terminal position, is identified in another reading frame (Covey et al., 1986, *Nucleic Acids Res.*, **14**, 623-633). Upstream of the *gag* domain, a motif of 182 nucleotides is detected which is repeated twice (Figure 1),

- the *pol* domain exhibits the conventional consensus of a retrovirus *pol* region at the level of the protease, reverse transcriptase and RNAse H domains. A motif close to the consensus **LLDTGA** is found in *pol* (Weber et al., 1988, Science, **243**, 928-931). The motifs **D** and **AF**, **LPQ** and **SP**, and **YVDD** (Xiong and Eickbush, 1990, EMBO J., **9**, 3353-3362) are respectively found in the 3rd, 4th and 5th homology boxes. The motifs **YTDGSS** and **TDS** are present in the RNAse H region,

- the *gag* and *pol* regions could be considered as being joined with a passage from the *gag* region to the *pol* region by a reading frame shift.

The present invention includes the sequences belonging to the HERV-7q family as defined above (presence of the SEQ ID NO: 1 sequence or of a homologous sequence or presence of both the sequences SEQ ID NO: 1 and SEQ ID NO: 2) and in particular the sequences SEQ ID NO: 3-22, 28 and 61; it also includes the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences as well as fragments derived from the coding regions of the preceding sequences corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences (SEQ ID NO: 37-57, 59-60 and 121-122).

These various fragments may be advantageously used as primers or as probes (reagents A); they hybridize specifically under high stringency conditions to a sequence of the HERV-7q family.

Among these fragments, the following fragments may be preferably mentioned:

- a fragment of 182 nucleotides, repeated twice, situated upstream of the *gag* domain at positions 2502-2611/2613-2865 of SEQ ID NO: 3:

<u>Primers and probes specific for the *gag* region</u>

- a sense primer G1F located in the region upstream of the *gag* domain of *HERV*-7q: 5'GGACCATAGAGGACACTCCAGGACTA3' (SEQ ID NO: 37);
- an antisense primer G1R located in the terminal 3' region of the *gag* domain: 5'CCTCAGTCCTGCTGCTGGATCATCT3' (SEQ ID NO: 38)
- the fragment of 1505 nt amplified by the pair G1F-G1R is used in order to generate the probes capable of hybridizing the various PCR amplification products:
  - a nested sense primer G2F: (SEQ ID NO: 39) 5'CCTCCAAGCAGTGGGAGGAAGAGAATT3'
  - a nested antisense primer G2R: (SEQ ID NO: 40) 5'CCTTCCCTGTGTTATTGTGGACATCATT3'
  - a nested sense primer G4F: (SEQ ID NO: 41) 5'GGAAGAAGTCTATGAATTATTCAATGATGT3'
  - a nested sense primer G3F: (SEQ ID NO: 42)

5'GGGACACAGAATCAGAACATGGAGATT3'

- a nested antisense primer G4R: (SEQ ID NO: 43)

5'GCCTTCAGAAGAGTCAGGTGACAGAGA3'

- a nested antisense primer G5R: (SEQ ID NO: 44)

5'GAGCCTCCAAAGTCCACTTGCCTGA3'

<u>Primers and probes specific for the *env* region</u>

- a sens primer E1F: (SEQ ID NO: 45)

5'GATTTCAGTATCTACTAGTCTGGGTAGAT3'

- an antisense primer E1R: (SEQ ID NO: 46)

5'CTAGGAAATCCAGCTAGTCCTGTCTCA3'

- the fragment of 2529 nt, amplified by the pair of primers E1F-E1R, is used to generate the probes capable of hybridizing the various PCR amplification products:

- a sense primer E2F: (SEQ ID NO: 47)

5'CCAAGACAGCCAACTTAGTTGCAGACAT3'

- an antisense primer E2R: (SEQ ID NO: 48)

5'GGACGCTGCATTCTCCATAGAAACTCTT3'

- a sense primer E3F: (SEQ ID NO: 49)

5'GCAATACTACATACACAACCAACTCCCAA3'

- an antisense primer E3R: (SEQ ID NO: 50)

5'GGGGGAGGCATATCCAACAGTTAGTA3'

- a sense primer E4F: (SEQ ID NO: 51)

5'CCATCTACACTGAACAAGATTTATACACTT3'

- an antisense primer E4R: (SEQ ID NO: 52)

5'AATGCCAGTACCTAGTGCACCTAGCACT3'

- a sense primer E5F: (SEQ ID NO: 53)

5'CGAATACAACGTAGAGCAGAGGAGCTTCGAA3'

- a sense primer E6F: (SEQ ID NO: 54)

5'AGCCCAAGATGCAGTCCAAGACTAAGAT3'

- a primer E5R: (SEQ ID NO: 55)

5'GCGTAGTAGAGGTTGTGCAGCTGAGAT3'

- a primer ExF: (SEQ ID NO: 56)

CCCTTACCAAGAGTTTCTATGGAGAAT

- a primer ExR: (SEQ ID NO: 57)

ACCGCTCTAACTGCTTCCTGCTGAATT

All the oligonucleotides are designed to be able to generate a sense primer and an antisense primer by a shift in the sequence of the reference primer of 1 to 7

nucleotides toward the 5' side or toward the 3' side; the modification of the sequence may cause a modification of the size of the primer of 1 to 7 nucleotides depending on the cases. The primers chosen may be optimized depending on the cases by shortening or extension affecting 1 to 9 nucleotides.

Preferably, the hybridization, cloning, subcloning, production, preparation and analysis of the nucleic acids, peptides and antibodies, the sequencing of the nucleic acids and peptides, the *in situ* hybridization and the immunohistochemistry are carried out under the conditions described in the following books:

- Current Protocols in Molecular Biology, Eds. F.M. Ausubel, R. Brent & R.E. Kingston et al. Green Publishing associates and Wiley Interscience.

- Molecular Cloning: a laboratory manual. Eds. J. Sambrook, E.F. Fritsch & T. Maniatis, Cold Spring Harbor Laboratory Press, Cold Spring Harbor.

- The Practical Approach series. Eds. D. Rickwood & B.D. Ames, IRL Press and Oxford University Press. In particular antibodies I & II; DNA cloning I, II, III; Nucleic acid and protein sequence analysis; Nucleic acid hybridization; Nucleic acid sequencing; Oligonucleotide synthesis; Protein purification applications; Protein purification methods; Protein sequencing; Transcription and translation; Gels electrophoresis of nucleic acids; Gels electrophoresis of proteins; Genome analysis; HPLC of macromolecules; Human genetic diseases; Microcomputing in biology; Molecular neurobiology; Mutagenicity testing; Essential molecular biology I & II.

- Proteome research: New frontiers in functional genomics, Eds. M.R. Wilkins et al., Springer.

The human endogenous retroviral sequence (SEQ ID NO: 3) situated on the long arm of chromosome 7 corresponds to the HERV-7q sequence; it has 10.5 kb

(Figs. 1 and 2) and satisfies the criteria defined above.

The search for domains exhibiting total or partial similarity with the *gag* and *env* regions of HERV-7q resulted in the identification of novel endogenous retroviral sequences. These sequences may have the structure of a complete endogenous retrovirus such as the endogenous retroviral sequence situated close to the gene for the alpha and delta subunits of the T cell receptor, and consequently called HERV-TcR; by way of example, Figure 7 shows the comparison of the nucleic alignments of the respective *gag* domains of HERV-7q and HERV-TcR (sequence HG12, SEQ ID NO: 19). Partial retroviral structures also exist. These retroviral domains, similar to HERV-7q, are identified in independent nucleic sequences as shown by their chromosomal location. Nucleic motifs (called here HEx or HGx, and analogous to *env* or *gag* type domains, respectively) resembling the *env* or *gag* domains of HERV-7q were found, with the aid of the abovementioned databases:

- HE2: chromosome 17 (SEQ ID NO: 4),
- HE3 and HG3: chromosome 6 (SEQ ID NO: 5 and 6),
- HE4: chromosome X (SEQ ID NO: 7),
- HE5: chromosome X q22 (SEQ ID NO: 8),
- HE6 and HG6: chromosome 1 q23.3-q24.3 (SEQ ID NO: 9 and 10),
- HE7: chromosome 7 p15 (SEQ ID NO: 11),
- HE8 and HG8: chromosome 19 (SEQ ID NO: 12 and 13),
- HE9: chromosome X (SEQ ID NO: 14),
- HE10: chromosome X q13.1-21.1 (SEQ ID NO: 15),
- HE11 and HG11: chromosome 7 q21-22 (SEQ ID NO: 16 and 17),
- HE12 and HG12, in HERV-TcR: chromosome 14 q11.2 (SEQ ID NO: 18 and 19),
- HE13 (SEQ ID NO: 61): chromosome 6 q24.1-24.3

The present invention also includes the coding and noncoding fragments for all or part of enverin

comprising at least 14 nucleotides and in particular the fragments encoding the C-terminal part of enverin, either from amino acid 291, or from amino acid 321, starting from the first methionine.

These fragments comprise in particular a critical zone where two inserts of 12 nucleotides were characterized:

- a first insert was identified (sequence A) in individuals of 2 groups (patients and controls). This insert, situated between amino acids 487 and 488, makes it possible to insert the tetrapeptide VLQM. A comparative analysis shows that this insert is identified in a homologous region situated in the sequence HE13, belonging to the HERV-7q family. The amplification of the HE13 type sequence could indicate that there is an impairment of the enverin sequence of HERV-7q, which would promote the amplification of the sequence contained in HE13. This observation also makes it possible to use this insert as a specific element for amplification of sequences of the HE13 type.

A second insert (sequence B) was identified in a patient with MS. The insert of 12 nucleotides is situated at the level of amino acid 495 and encodes the tetrapeptide MQSM. It is remarkable to observe that this insert is also identified in a homologous region situated in HE13.

Sequence A: TAAACTACAAATGGTTCTTCAAATGGAGCCCA (SEQ ID NO: 59)

Sequence B: GATGCAGTCCAAGATGCAGTCCATGACTAAGA (SEQ ID NO: 60).

These observations demonstrate modifications of the enverin sequence of the HERV-7q type which constitute the basis for a detection strategy by allele-specific amplification (AS-PCR), making it possible to detect these differences in a population and which could correspond either to a mutation/deletion associated with a degree of susceptibility, or to a polymorphism, or to a

mutation/deletion associated with a pathological condition such as multiple sclerosis.

The alignments of the *env* (Fig. 8) and *gag* (Fig. 9) domains explain the levels of homology observed between the sequences described above and the homologous sequences in HERV-7q. The analogies can extend to the flanking retroviral motifs.

Analysis of the sequence tags available in databases shows that transcripts belonging to some members of this family, in particular HERV-7q, are essentially expressed in tissues of foetal or placental origin.

Polypeptide sequences generated by these transcripts can therefore be potentially produced and biological functions or activities can be envisaged, by analogy with biologically active polypeptides of viral or retroviral origin; for example, the peptide motifs of the CKS-17 type (Haraguchi et al., PNAS, 1995, <u>92</u>, 5568-5571) (Fig. 5) or CKS-25 type (Huang S.S. and Huang J.S., J. Biol. Chem. 1998, 273, 4815-4818) which have immuno-modulatory functions on the lymphocytic host cells. The differences in sequence which are observed and possible normal or pathological modifications are in particular responsible for modulation of the function.

HERV-7q represents the paradigm of the novel family of human endogenous retroviral sequences or of endogenous retroviral motifs.

HERV-7q and some of the endogenous retroviral sequences belonging to its family have a *pol*-type domain analogous to *pol*-type retroviral sequences such as for example the *pol* region identified in the MSRV retrovirus associated with multiple sclerosis and described by H. Perron et al. (1997, *Proc. Natl. Acad. Sci.* USA, **94**, 7583-7588; International Application PCT WO 97/06260).

However, the sequences according to the present invention are distinguishable from the infectious exogenous retroviral sequences analogous to MSRV

previously described in that the *gag* and *env* sequences according to the invention are significantly different according to the criteria defined above and as a function of certain specific characteristics, for example the long open reading frame of the *env* domain of HERV-7q; they would be able to allow the signaturing of a pathological condition when they have insertions, deletions, reading frame shifts or mutations.

Indeed, the differences observed between the human sequences of the HERV-7q type, which are isolated from individuals reputed to be normal, and the sequences derived from some samples of pathological origin are not randomly distributed. Comparisons carried out between the *gag* region obtained from infectious retroviral particles (EMBL accession No.: A60168, A60200, A60201, A60171 and the like) and the corresponding *gag* sequence of HERV-7q (Fig. 9), make it possible to observe that the mutations preferably affect non-sense codons. For example, two non-sense codons in HERV-7q are replaced by an arginine codon in A60200, which makes it possible to obtain a deduced sequence of 109 amino acids for HERV-7q and of 166 amino acids for A60200. The base changes consequently make it possible to extend the reading frame and to potentially encode larger sized polypeptide structures (Figure 10).

Likewise, an *env*-type sequence obtained from infectious retroviral particles exhibits a significant analogy with the *env* domain of HERV-7q (Figure 11). These marked analogies between exogenous and endogenous retroviral sequences could be responsible for the triggering or worsening of certain pathological processes, in particular certain autoimmune diseases such as multiple sclerosis. In this regard, it is possible to note that certain endogenous retroviral sequences described in the invention are situated close to or in regions reputed to exhibit susceptibility for multiple sclerosis: for example HERV-7q and the 7q21-22 region of chromosome 7, likewise for HE12 and HG12 in

HERV-TcR and the region of the gene encoding the alpha and delta chains of the T cell receptor, HE2 and chromosome 17, or HE3, HE13 and HG3 and chromosome 6, for example, the sequences HE11 and HG11, around the region 7q 21-22 or HE4, HE5, HE6, HE9, HE10 or HG10 on the X chromosome. These sequences would therefore be capable of providing the means for locating or identifying the genes for predisposition.

No significant homology is observed with endogenous retroviral sequences already described; on the other hand, a limited homology may be noted, which makes it possible to identify a general structure of the *env* domain; however, said homology is less than the criteria defined according to the invention between the *env* domains of the sequence HERV-7q (SEQ ID NO: 1) and the sequence HERV-9 (Figure 12). Figure 11 shows extensive homologies between the sequence HERV-7q with an exogenous retroviral sequence (accession No. EMBL: A60170).

The human endogenous retroviral sequences belonging to the HERV-7q family can protect against attacks linked to the environment or can be beneficial for the individual. This beneficial effect could be one of the possible reasons for the selection pressure exerted on some of these sequences and the potentially functional character of the deduced protein structures identified: for example the long open reading frame capable of encoding a novel protein and corresponding to the *env* domain of HERV-7q.

The human endogenous retroviral sequences belonging to the HERV-7q family could be associated, for example, with pathological conditions related to processes linked to cancer, to neuropathological conditions with an autoimmune component or to any other pathological process in association or otherwise with endogenous or exogenous viruses or retroviruses. Their action could be related to the outbreak, the worsening, the modification of the time of appearance or the protection against the disease.

In the context of application to autoimmune pathological conditions (such as for example lupus, Sjögren's syndrome, rheumatoid arthritis, multiple sclerosis and the like), significant analogies may be detected between the endogenous retroviral motifs identified and motifs found in retroviral structures characterized in patients with autoimmune pathological conditions such as multiple sclerosis; for example, fragments of *gag* domain (recently available in databases) obtained from infectious retroviral particles or the complete sequence of the *pol* domain corresponding to the MSRV virus associated with multiple sclerosis. These retroviral motifs possess significant analogies with homologous endogenous sequences of the HERV-7q type, which makes it possible to envisage direct or indirect association with pathological processes, including multiple sclerosis, in association or otherwise with MSRV.

The importance of these sequences goes beyond the context of autoimmune diseases. Apart from the general importance of retroviral motifs in the triggering or worsening of a tumor process, which is well established in particular in murine models (H. Fan in *The retroviridiae*, 1994, ed. J.A. Levy, Plenum, New York, p. 313-353), these sequences could be present close to or inside important genes and could alter the expression thereof: for example HERV-TcR and the genes for the alpha and delta subunits of the receptor for the T cells involved in disruptions of the immune system.

The present invention includes, in addition, the use of sequences combined with the sequences of the HERV-7q family for the detection and/or prognosis of various autoimmune diseases (neuropathological conditions in particular); these sequences encode all or part of a factor whose function, the regulation/de-regulation or alteration (polyadenylation, alternative splicing), is associated with the normal or pathological expression or with the regulation/de-

regulation of the motifs belonging to the HERV-7q family and correspond to transcripts or cDNAs of the nucleotide sequences encoding genes situated in regions flanking or delimiting retroviral sequences of the HERV-7q family.

The expression flanking region is understood to mean any region situated close to (contained in or including) an endogenous retroviral sequence belonging to the HERV-7q family, as defined above, up to and including the genes immediately contiguous and/or situated at a distance which cannot exceed 120 kb.

The inventors have now found that the presence of the retroviral sequences as defined above disrupts the expression or impairs the structure of the flanking sequences defined below.

The transcripts of said flanking sequences (and fragments thereof, in particular those underlined or in italics in Figures 14-16, 22-26, as defined below:

- at 1021 bp upstream of HERV-7q, there is identified an endogenous retroviral sequence called RH7 (SEQ ID NO: 62 and Figure 22); this sequence is situated in 5′ of the HERV-7q sequence; in Figure 22, the portion in italics corresponds to the beginning of the HERV-7q sequence; the RH7 sequence is underlined; two putative polyadenylation sites are in bold. This sequence SEQ ID NO: 62 exhibits significant homology, on more than 6 kb, with RGH-type endogenous retroviral sequences (Figure 13). Sequences belonging to this family are expressed in particular in patients with rheumatoid osteoarthritis (Nakagawa et al., (1997), Arthritis, Rheum., 40, 627-638). The present invention also includes fragments of the sequence SEQ ID NO: 62, comprising between 14 and 50 nucleotides (used as primers), preferably between 14 and 25 nucleotides, or at least 25 nucleotides (used as probe), which fragments have the following characteristics: the 4 nucleotides of the 3′ end are different from the corresponding motifs of the sequence RGH2 (bottom sequence in Figure 13, GenBank accession No.: D110 18),

- at less than 9 kb upstream of HERV-7q, there is identified the sequence RAM75 (SEQ ID NO: 63 and Figure 14) containing the 24 coding exons (which cover close to 41 kb) of the gene for peroxisomal ATPase PEX1. PEX1, in combination with PEX6, is responsible for the import of peroxisomal proteins and for stabilizing the PEX5 receptor. A disruption/alteration affecting PEX1 is responsible for various neuropathological conditions such as Zellweger syndrome, neonatal adrenoleukodystrophy and the infantile form of Refsum's disease (Reuber et al., (1997), Nature Genet., 17, 445-448). It can be recalled that the main function of the peroxisomes is associated with the metabolism of fatty acids, in particular by β-oxidation processes. Impairment of the gene identified in the sequence RAM75, or of its expression, by modification of the function of the regulatory 5' and 3' regions or by modification of the splicings or of the polyadenylation processes, in particular under the influence of neighboring retroviral motifs, would be able to disrupt the expression and the structure of ATPase and consequently to disrupt one of the peroxisomal functions, in particular the metabolism of lipids, in particular myelin lipids, with consequences for certain pathological conditions, including neuropathological conditions such as multiple sclerosis; the underlined portions (Figure 14) correspond to the 24 coding exons.

The present invention also includes the fragments of the sequence SEQ ID NO: 63, included in the abovementioned 24 coding exons and comprising at least 14 nucleotides.

Analysis of the expression profile (transcripts and proteins) of the sequence RAM75 (SEQ ID NO: 63) is a good indicator for the differential diagnosis of neuropathological conditions with an autoimmune component.

In Figure 14, the coding exons are underlined. The initiation and non-sense codons as well as the

putative polyadenylation sites are in bold and underlined;

- at 0.7 kb downstream of the sequence HERV-7q and on nearly 17 kb (SEQ ID NO: 64 and Figure 15), there is identified the nucleotide sequence RAV73, where there are detected sequence tags and potential exons capable of producing one or more polypeptide sequences; the invention also includes fragments of this sequence SEQ ID NO: 64 included in the sequence tags and the potential exons as they appear (portions underlined) in Figure 15, which fragments comprise at least 14 nucleotides,

- at 120 kb upstream of the sequence HG3, and on 15 kb, there is the nucleotide sequence RBP3 (SEQ ID NO: 65 and Figure 23), which covers the 3' end of the gene encoding a transcription factor of the Blimp-1 family (SEQ ID NO: 119 and Figure 25), a protein of 789 amino acids which is a repressor of the expression of the interferon-beta gene (Keller and Maniatis, Genes Dev., (1991), 5, 868-879), which is already associated with certain malignant pathological conditions (Mock et al., Genomics, (1996), 37, 24-28), and which could play a role in the differentiation and the pathogenesis of B cells. The possible association of the endogenous retroviral sequence containing the motifs HG3 and HE3 and of Blimp-1 has many benefits, in the case of pathological conditions, and in particular multiple sclerosis. Blimp-1 acts in particular on the B cells whose contribution in inflammatory processes associated with multiple sclerosis is known. Blimp-1 is capable of blocking the viral induction of the INFβ promoter whose capacity to reduce the frequency of attacks and the progression of lesions in patients with MS is known. Disruption in the expression or the structure of Blimp-1, in relation to a retroviral element of the HERV-7q type, is consequently associated with neuropathological conditions or with diseases having an autoimmune character, such as multiple sclerosis; this nucleotide sequence RBP3 (SEQ ID

NO: 65) contains nucleotide motifs identified in the nucleic sequence encoding the Blimp-1 gene; the invention also includes the detection of the mRNA sequences for the Blimp-1 protein (SEQ ID NO: 119),

- the endogenous retroviral sequence of the HERV-7q type, containing HE3 and HG3, is situated in the HI3 region corresponding to an intron extending over more than 46 kb (SEQ ID NO: 66), of a gene which could encode the analogue of APS (Figure 24), a protein of 275 amino acids specific to apoptosis, overexpressed in various cells in culture after triggering an apoptotic process (Hammond et al., FEBS Lett., (1998), 425, 391-395). The intron is situated at the level of amino acid 231 of APS. The end of HE3 is at more than 12 kb from the 5′ end of the intron, whereas HG3 is situated at more than 28 kb from the 3′ end of the intron. Apoptotic processes are associated with multiple sclerosis. In particular, there has been described an apoptotic process affecting astrocytes and oligodendrocytes in the presence of a purified fraction of cerebrospinal fluid of patients suffering from multiple sclerosis (Ménard et al., J. Neurol. Sci., (1998), 154, 209-221).

Finally, it should be stressed that the nucleic region containing HE3, HG3, HI3 and RBP3 is located at the level of the short arm of chromosome 6, in 6p21, which is a proposed region of susceptibility to multiple sclerosis (The Multiple Sclerosis Genetic Group, Nature Genet., (1996), 13, 469-472).

The interaction between the HERV-7q type sequences and the flanking sequences and the importance of establishing a profile of expression including one or more of the abovementioned sequences in order to establish a differential diagnosis of a neuro-pathological condition is even more evident because it is observed that the sequences HG12 and HE12 are situated in an intron region of the gene encoding the alpha and delta subunits of the T cell receptors. The T cell receptors are involved in the immune regulation

process and their influence has been proposed in the case of autoimmune diseases, including multiple sclerosis.

The subject of the invention is also transcripts generated from the abovementioned sequences as well as those optionally exhibiting modifications in the reference sequences described in the invention when they are expressed in certain patients.

Indeed, the systems for regulating the the expression of the retroviral proteins of HERV-7q, which are present in the LTR type motifs, could influence the expression of genes situated in the close or distant chromosomal vicinity and could induce disruptions of an immunological and/or neurological character. For example, the endogenous retroviral sequence HERV-TcR exists in the immediate vicinity of the genes for the alpha and delta subunits of the T cell receptor previously described. The LTR-type motifs could also encode superantigens (Acha-Orbea and Palmer, 1991, *Immunol. Today*, **12**, 356-361). In general, retroviral proteins of the HERV-7q or related type, or their truncated or partial forms could be involved in cytotoxicity or superantigenicity phenomena, such as for example those derived from the long open reading frame identified in the *env* domain (Figure 4).

Sequences of the HERV-7q 5′ and 3′ LTR type, which are highly conserved, are involved in such regulatory effects. By way of example, LTX is described, which is a sequence comparable to that of an HERV-7q LTR (SEQ ID NO: 67 and Figure 16), and which is present in the center of an intron of more than 49 kb, but at 2 kb from the donor 5′ site of the FMR2 gene associated with fragile X and encoding a protein of 1311 amino acids (Figure 26). The LTRs modulate the alternative splicing (Kapitonov and Jurka, (1999), J. Mol. Evol., 48, 248-251), the expression of the gene, the binding to nuclear proteins (Akopov et al., (1998), FEBS Lett., 421, 229-233), or allow the

production of an alternative polyadenylation signal (Goodchild et al., (1992), Gene, 121, 287-294).

In general, there may be noted the existence of several endogenous retroviral sequences of the HERV-7q type (HE4, HE5, HE9, HE10), situated at the level of chromosome X which represents the chromosome associated with the largest number of pathological conditions.

In this regard, it is possible to note that retroviral motifs derived from defective regions are capable of having biological functions; for example, the envelope protein p15E, derived from defective retroviral motifs, possesses an anti-inflammatory and immunosuppressive activity (Snyderman and Ciancolo, 1984, *Immunol. Today*, 5, 240-244).

These structures are probably capable of causing breaks or of amplifying deregulations in the immune defense processes. Some of the motifs of the *gag, env* and LTR-type domains may be associated with a particular function or may contribute to the normal or pathological function of the flanking domains as defined above (SEQ ID NO: 62-67). Recombinations with an element of exogenous, retroviral origin or otherwise can give rise to the production of nucleic or protein motifs which could either protect or trigger or promote or worsen a pathological condition. Likewise, a retroviral structure containing endogenous retroviral elements according to the invention would be capable of causing a pathological process after passing through an exogenous transient cycle followed by reintegration into a sensitive or critical region of the human genome.

It is thus possible to obtain expression profiles (transcripts and optionally proteins) which correspond to the abovementioned neuropathological conditions.

Likewise, the combination of motifs belonging to the HERV-7q family, or of elements induced by motifs belonging to the HERV-7q family, with motifs of exogenous origin or induced exogenously would be

capable of triggering or worsening a pathological process or on the contrary of promoting protection or partial remission or a complete and permanent cure.

The detection made possible of the HERV-7q type domains suggests possible applications at the prophylactic, prognostic and diagnostic level; for example, immunological approaches or gene amplification, which make it possible to compare normal individuals serving as reference with patients, would be capable of promoting screening, of improving early detection of the outbreak of the disease and/or of monitoring the progression of a pathological condition in patients which may exhibit a susceptibility or in whom there has been an outbreak of the disease or in individuals considered to be normal, based on current clinical criteria.

The specific nucleic and immunological probes, as defined, in the present invention are capable of promoting the identification and detection of motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune pathological conditions, at the forefront of which is multiple sclerosis.

The subject of the present invention is also hybrid nucleic sequences, characterized in that they comprise sequences or motifs belonging to the HERV-7q family, or of elements induced by motifs belonging to the HERV-7q family, with motifs of exogenous origin or induced exogenously (exogenous retroviral sequences); such hybrid sequences are probably capable of triggering or worsening a pathological process or on the contrary of promoting protection or partial remission or a complete and permanent cure.

The subject of the present invention is also a diagnostic reagent for the differential detection of complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that

it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate marker as well as of sequences as defined in Figures 18-21.

The sequences of the nucleic, ribonucleic and oligonucleotide probes used will be chosen from the *env* and *gag* regions or their flanking regions; for example the oligonucleotide primers for HERV-7q will be chosen from the regions situated between nucleotides 3065 and 4390, nucleotides 6965 and 9550 or nucleotides 2502-2865 of SEQ ID NO: 3, as well as from any adjacent sequence (upstream or downstream) capable of allowing specific amplification (Figure 1).

Among the appropriate markers, there may be mentioned radioactive isotopes, enzymes, fluorochromes, chemical markers (biotin), haptens (digoxygenin) and antibodies or appropriate base analogues.

Preferably:

- said reagent is selected from the sequences SEQ ID NO: 37-57 and is capable of being used as a primer,

- said reagent is selected from the following sequences:

a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),

a fragment of 2529 nt amplified by the pair of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R),

a fragment of 182 nucleotides, repeated twice, situated upstream of the *gag* domain at positions 2502-2611/2613-2865,

fragments encoding or not encoding all or part of enverin, comprising at least 14 nucleotides and in particular the fragments encoding the C-terminal portion of enverin, either from amino acid 291, or from amino acid 321, starting from the first methionine,

and is capable of being used as a probe.

The subject of the present invention is also a method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the *env* or *env* and *gag* type, their normal or pathological variants, by hybridization and/or gene amplification, carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analysed is brought into contact with at least one probe as defined above, and

(b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

In accordance with said method, it may comprise:

* prior to step (a):

. a step of preparing the relevant biological tissue or fluid,

. a step of extracting the nucleic acid to be detected, and

. at least one gene amplification cycle, and

* subsequent to step (b):

. a step of comparing the nucleic sequences obtained in said biological sample with the human endogenous retroviral sequences according to the invention by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a deletion or a single mutation between the various sequences compared.

In accordance with the invention, the human endogenous retroviral sequences according to the invention are thus compared with the nucleic sequences present in the biological sample to be analysed and allow the detection of homologous sequences from patients suffering from pathological conditions likely to involve a modification of their genome.

Advantageously, said gene comparisons are carried out using genomic DNA obtained from control individuals and from patients.

A conventional gene amplification by PCR will be carried out with the aid of 5'-sense and 3'-antisense primers delimiting or comprising the zone to be studied (*env* zone or *gag* zone).

Also advantageously, the sequences of the nucleic, ribonucleic and oligonucleotide probes used are chosen from the *env* and *gag* regions or their flanking regions; for example the oligonucleotides which are primers for HERV-7q will be chosen from the regions situated between nucleotides 3065 and 4390 and nucleotides 6965 and 9550, and from any adjacent sequence (upstream or downstream) capable of allowing specific amplification (Figure 1), as specified above. They are preferably selected from the group consisting of

a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),

a fragment of 2529 nt amplified by the pair of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R).

The gene amplification step is in particular carried out with the aid of one of the following gene amplification techniques: amplification using Qβ-replicase, PCR, LCR, ERA, CPR or SDA.

The subject of the present invention is also chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence as defined above combined with an endogenous

retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides, as defined above.

The subject of the present invention is also a method of detecting transcripts as defined above, characterized in that it comprises:

- collecting messenger RNAs obtained from control biological samples (biological tissues, cells or fluids) and from a similar sample collected from patients, and

- the qualitative and/or quantitative analysis of said mRNAs by *in situ* hybridization, by dot-blot, Northern blotting, RNAse mapping or RT-PCR, with the aid of a diagnostic reagent as defined above.

The subject of the present invention is also a method for the detection and/or evaluation of an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, characterized in that it comprises:

- depositing on an appropriate support, such as for example a nylon filter, a glass slide or their equivalent, cDNA or its equivalent obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or from specific oligonucleotide sequences, said DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, as defined above, consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/de-regulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family and in

which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as defined above,

- the hybridization of said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and

- the detection of the hybrids formed.

According to an advantageous embodiment of said method, said transcript or cDNA is selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

According to another advantageous embodiment of said method, said support comprises, in addition, any endogenous or exogenous retroviral sequence.

The method of DNA chips (Bowtell, (1999), Nature Genet., 21, 25-32), is used to evaluate the modification of the expression of all or part of some of the sequences of retroviral origin of the HERV-7q type and flanking sequences. Briefly, DNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or specific oligonucleotide sequences are deposited on a support, such as for example a nylon filter, a glass slide or their equivalent. The deposited nucleic sequences cover the various retroviral domains described above, as well as the contiguous sequences and the flanking genes. In order to detect possible alternative splicing processes, specific DNAs are synthesized per step of 500-600 nucleotides with an overlap of 250-300 nucleotides on either side. The alternative splicings already identified will be the subject of a specific synthesis. The hybridization is carried out with the

aid of a probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, members of the various ethnic populations, patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, including multiple sclerosis. In this case, a µg fraction and up to a few µg of mRNA or up to a few µg or a few tens of µg of RNA, depending on the method used and the size of the DNA chip involved, are sufficient for the synthesis of the nucleic probe. The nucleic probe is suitably labeled so as to allow subsequent detection, such as for example by fluorescence or by an equivalent method.

The use of bi- or even multicolored probes makes it possible to specify the concerted expression of several genes in parallel, while taking advantage, furthermore, of a precise normalization. The results are acquired automatically, such as for example by a laser scanning system or its equivalent.

Two types of DNA chips are designed, on the one hand chips having an exhaustive set of sequences, and on the other hand specific DNA chips enabling targeting to a more specific application.

For example, a critical sequence in that it would contain a difference relating to a deletion or even a mutation is detected with the aid of specific oligonucleotides (Wang et al., (1998), Science, 280, 1077-1082). The polymorphism associated with a base or with a mutation is detected with the aid of four oligonucleotides possessing one of the four sequence possibilities at the level of a base (A, C, G or T); for each point difference, the 4 oligonucleotides are deposited and the hybridization intensities are compared. Furthermore, an alternative splicing is detected using DNAs corresponding to a single effective or putative exon; the gene is therefore analyzed exon by exon. The DNA chips also relate, by extension, to

any endogenous or exogenous retroviral sequence, such as for example ERV-9, ERV-K, ERV-L, ERV-H, ERV-4, ERV-6, ERV-8, ERV-10, ERV-15, ERV-16, ERV-17, ERV-18, ERV-21, ERV-24, ERV-33, ERV-34, ERV-36, ERV-40, ERV-42, ERV-MLN, ERV-FRD, ERV-FTD and the like), as well as all the putative exon sequences (identified by the existence of sequence tags and corresponding transcripts) or effective exon sequences, and which are situated on either side up to a distance of 120 kb of the endogenous retroviral sequences of the HERV-7q type.

The comparative study is carried out between a control sample and the sample to be tested, in a prophylactic, diagnostic or therapeutic perspective, such as for example the early detection of a modification of the expression of one of the sequences, in a cell, a tissue or an organism, the identification of a sequence associated with a susceptibility or with any pathological condition, the monitoring of the progression of the pathological condition or the monitoring of a treatment and the evaluation of its efficacy.

Apart from the applications already mentioned, the advantage of the method makes it possible, more generally, to make an assessment of the changes observed in an individual, which constitutes to a certain extent an identity card, which facilitates an epidemiological approach which makes it possible to establish novel correlations between a particular observed profile and a pathological condition, in the absence of an *a priori* regarding this pathological condition.

The subject of the present invention is also a kit for the detection and/or evaluation of an auto-immune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in addition to the buffers necessary for carrying out the methods as defined above:

- diagnostic reagents A as defined above, and

- reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/de-regulation or alteration is associated with the normal or pathological expression or with the regulation/de-regulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

According to an advantageous embodiment of said kit, said reagents B are selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, as well as the sequences represented in Figures 13-17, 22-26.

The subject of the present invention is also products of translation, characterized in that they are encoded by a nucleotide sequence as defined above.

The subject of the present invention is also a peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO: 1-22, 28 and 61, as defined above, according to the combinations offered by the use of the various possible reading frames (see also Figures 18-21).

Said peptide also includes the derived peptides or polypeptides comprising between 5 and 540 amino acids (SEQ ID NO: 23-36 and SEQ ID NO: 58 and their fragments of at least 5 amino acids) and in particular a fragment of 538 amino acids, starting at the first methionine of the sequence SEQ ID NO: 26 (enverin).

According to an advantageous embodiment of said peptides they are in particular selected from the

sequences SEQ ID NO: 23-36, 58, in particular the sequence SEQ ID NO: 26 and its C-terminal fragments, either from the amino acid 291, or from the amino acid 321, starting from the first methionine.

According to another advantageous embodiment of said peptides, they are obtained from nucleic sequences as defined above, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).

The invention thus includes the deduced peptides or the deduced proteins corresponding to all or part of the nucleic sequences described in the invention, and optionally exhibiting modifications with the reference sequences described in the invention, when they are expressed in some patients. In particular, the invention includes the complete or partial sequences obtained according to the 3 sense reading frames and the 3 reverse and complementary reading frames (see Figures 18-21).

Advantageously, the analysis of the structure of the env domain of HERV-7q, called enverin, made it possible to demonstrate successively:

- an N-terminal signal peptide (region 1-21) and two transmembrane domains (region 320-340; 455-477), responsible for interactions with membrane lipid or protein motifs,

- an immunomodulatory motif of the CKS-17 (Haraguchi et al., (1995), 92, 5568-5571)/CKS-25 type. It is possible to note, in this regard, the presence of an **RalD** motif inside the peptide of the CKS-17/CKS-25 type of HERV-7q and a motif **RvaD** at position 363 which correspond to the consensus W/RxxD, proposed for the active site of the TGF-βs (Huang et al., J. Biol. Chem., 1997, 272, 27155-27159), potent factors associated with growth, with differentiation and with morphogenesis and which are associated with many human pathological conditions, such as tumor processes (Tang

et al., (1998), Nat. Med., 4, 802-807) or neuro-degenerative diseases (Flanders et al., (1998), Prog. Neurobiol., 54, 71-85). The peptides according to the invention containing these motifs can advantageously serve as antagonists by inhibiting the attachment of the TGF-βs to their natural receptors,

- N-glycosylation motifs. The glycosylation of the envelope proteins of retroviruses appears to be directly associated with their functional properties, for example by influencing the number of determinants available in the T cells or by promoting recognition of antigens by the T cells. Glycosylation could play a role in the outbreak or the spread of a pathological condition with an autoimmune component. The glycosylations are necessary for maintaining the conformation of certain epitopes, in particular during the production of a recombinant envelope protein so as to develop a diagnostic reagent and to promote the efficacy of a possible vaccine. Positions 171, 210, 216, 236, 244, 283 and 411. Expected number at random: 3.2

- <u>prenylation sites</u>. Prenylation is an essential mechanism for attachment to the cell membrane and for the targeting of certain proteins. This targeting process could be essential for the production of specific therapeutic agents capable of interfering with the production and regulation of the traffic of cellular complexes calling into play proteins involved in the cell interactions, growth and movement. Positions 188 and 290. Expected number at random: 1.8

- <u>targeting sites in the endoplasmic reticulum</u>. These sites could make it possible to bring about the targeting toward the endoplasmic reticulum in order to carry out the modifications necessary for promoting membrane crossing. Positions 353 and 431. Expected number at random: 0.2

Moreover, the inventors have shown that a number of peptides derived from the env protein of HERV-7q (enverin) have a high affinity/half-life for

the class I HLA alleles. CADD analysis has made it possible to select candidate peptides, for which the best scores are indicated in Table I:

TABLE I

Location	Sequence	HLA molecule	Score	Sequence No.
399	FLGEECCYYV	A-0201	7214	SEQ ID NO: 68
462	LLFGPCIFNL	A-0201	1792	SEQ ID NO: 69
189	CLPLNFRPYV	A-0201	1453	SEQ ID NO: 70
439	GLLSQWMPWI	A-0201	488	SEQ ID NO: 71
263	CLPSGIFFV	A-0201	5103	SEQ ID NO: 72
444	WMPWILPFL	A-0201	897	SEQ ID NO: 73
252	IRWVTPPTQI	B-2705	3000	SEQ ID NO: 74
432	LRNTGPWGLL	B-2705	2000	SEQ ID NO: 75
158	LRTHTRLVSL	B-2705	2000	SEQ ID NO: 76
316	KRVPILPFVI	B-2705	1800	SEQ ID NO: 77
25	CRCMTSSSPY	B-2705	1000	SEQ ID NO: 78
137	TRVHGTSSPY	B-2705	1000	SEQ ID NO: 79
124	AREKHVKEVI	B-2705	600	SEQ ID NO: 80
478	SRIEAVKLQM	B-2705	600	SEQ ID NO: 81
442	SQWMPWILPF	B-2705	500	SEQ ID NO: 82
405	CYYVNQSGI	Kd	2400	SEQ ID NO: 83
346	FYYKLSQEL	Kd	2400	SEQ ID NO: 84
244	TYTTNSQCI	Kd	2400	SEQ ID NO: 85
291	SFLVPPMTI	Kd	1600	SEQ ID NO: 86
406	YYVNQSGIV	Kd	1200	SEQ ID NO: 87
167	LFNTTLTGL	Kd	1152	SEQ ID NO: 88
463	LFGPCIFNL	Kd	960	SEQ ID NO: 89
253	RWVTPPTQI	Kd	480	SEQ ID NO: 90
449	LPFLGPLAAI	B-5102	2200	SEQ ID NO: 91
3	LPYHIFLFTV	B-5102	1210	SEQ ID NO: 92
331	GALGTGIGGI	B-5102	798	SEQ ID NO: 93
321	LPFVIGAGVL	B-5102	550	SEQ ID NO: 94
499	RRPLDRPAS	B-2705	600	SEQ ID NO: 95
194	FRPYVSIPV	B-2705	600	SEQ ID NO: 96
383	RRALDLLTA	B-2705	600	SEQ ID NO: 97
39	WRMQRPGNI	B-2705	600	SEQ ID NO: 98
423	DRIQRRAEEL	B14	1800	SEQ ID NO: 99
158	LRTHTRLVSL	B14	600	SEQ ID NO: 100
359	ERVADSLVTL	B14	540	SEQ ID NO: 101
463	LFGPCIFNLL	Kd	1658	SEQ ID NO: 102
345	QFYYKLSQEL	Kd	1152	SEQ ID NO: 103
443	QWMPWILPFL	Kd	691	SEQ ID NO: 104
405	CYYVNQSGIV	Kd	500	SEQ ID NO: 105
474	NFVSSRIEAV	Kd	480	SEQ ID NO: 106
221	GPLVSNLEI	B-5102	1320	SEQ ID NO: 107
190	LPLNFRPYV	B-5102	726	SEQ ID NO: 108
449	LPFLGPLAAI	B-5101	1144	SEQ ID NO: 109
488	EPKMQSKTKI	B-5101	968	SEQ ID NO: 110
3	LPYHIFLFTV	B-5101	629	SEQ ID NO: 111
125	REKHVKEVI	Kk	1000	SEQ ID NO: 112
312	KPRNKRVPIL	B7	800	SEQ ID NO: 113
378	VVLQNRRAL	Db	792	SEQ ID NO: 114

Location	Sequence	HLA molecule	Score	Sequence No.
377	AVVLQNRRAL	Db	660	SEQ ID NO: 115
321	LPFVIGAGV	B-5101	629	SEQ ID NO: 116
304	DLYSYVISK	A3	540	SEQ ID NO: 117
301	TEQDLYSYVI	Kk	500	SEQ ID NO: 118

This Table I indicates an estimation of the dissociation half-life of a peptide of enverin with an allele of the class I HLA system (the tables of Parker coefficients: J. Immunol, (1994), 152, 163-175). The location indicates the position of the first amino acid of the peptides tested in the enverin sequence. The one-letter code is used for the amino acid sequence. The scores around 500 or greater than 500 were selected. By way of comparison, an analysis was carried out on a concatenation of peptides (polypeptide of 4968 amino acids) reputed to bind the molecules of the class I major histocompatibility complex (Rammensee, Immunogenetics, (1995), 41, 178-228); the ten best scores recorded for nonapeptides and the HLA type A_0201 are respectively 4984, 4047, 2406, 1267, 800, 705, 607, 591, 591 and 577.

It can be seen from this Table I that some molecules of the type I major histocompatibility complex are capable of binding peptides derived from enverin, thus assimilated with peptides of viral or tumor origin, at the level of the endoplasmic reticulum. The complexes formed at the level of the endoplasmic reticulum are then transported to the cell surface, which causes the destruction of the target cell by the cytotoxic T lymphocytes. The peptides identified generally comprise 8 to 10 amino acids. Studies have shown that some alleles of the class I HLA system are thus associated with certain pathologies, in particular with an autoimmune character, such as HLA-B27 with rheumatoid spondylitis or HLA-B51 with Behçet's disease.

A peptide capable of binding a particular class I molecule is consequently capable of functioning as a T cell epitope.

Consequently, the present invention also includes the fragments 399-471 and 244-271 of enverin which advantageously group together several epitopes having high affinity for various haplotypes of the class I HLA system. The use of all or some of these polypeptides is consequently capable of promoting an increase in the T cell repertoire, by allowing better efficacy of the immune response in the context of the various immunotherapeutic, prophylactic or vaccine strategies. These polypeptides may be advantageously delivered for example by the use of viral vectors, viral or synthetic particles, lipopeptides, conventional adjuvants, naked nucleic acids or nucleic acids adsorbed on particles, or liposomes.

For the purposes of the present invention, the peptides may be chemically or biochemically modified; some of the amino acids may be replaced with an analogous amino acid, according to conventional criteria for homologies (A or G; S or T; I, L or V; F, Y or W; N or Q; D or E).

The subject of the present invention is also immunogenic or vaccine compositions for protecting against autoimmune diseases, in particular in at-risk subjects, characterized in that it comprises at least one peptide comprising at least one motif of the CKS type and/or at least one peptide consisting of a motif having affinity with one of the haplotypes of the class I or class II HLA system and a pharmaceutically acceptable vehicle.

According to an advantageous embodiment of said composition, said motif is selected from the group consisting of peptides, as defined in Table I above.

According to another advantageous embodiment of said composition, said peptide has the following sequence:

sequence CKH: <u>LQNRRALDLLTAERGGTcl</u>**FLGEECCYYV** (SEQ ID NO: 120).

It is remarkable to note at the level of position 380 of the enverin protein, the contiguousness

of the motifs of the CKS-17 type (underlined) and of the peptide having the highest score (in bold; see peptide at position 399 in Table I, SEQ ID NO: 68) in the sequence CKH.

The clonal activation of the subgroups of lymphocytes, for example of cytotoxic lymphocytes, by the peptides in Table I and by extension their homologues, is blocked by conventional immunotherapy means such as for example serotherapy and vaccination.

The combination of two sequences or of the sequences analogous to the CKH peptide (SEQ ID NO: 120), is capable of causing a synergistic process in the immune response, which could bring into play additional signaling and activation pathways capable of modulating the lymphocyte activation.

The vaccination relates to the production of antibodies directed against the peptides of Table I, according to the rules of the prior art and according to the methods of release controlled by artificial or cellular implants using a composition as defined above and by using gene therapy means, such as for example expression of nucleic sequences encoding the peptides of Table I. Consequently, the subject of the invention is also immunogenic or vaccine compositions, characterized in that they comprise a vector including at least one nucleic sequence encoding a peptide as defined in Table I, optionally combined with a sequence encoding a motif of the CKS-17 type.

The serotherapy relates to the use of neutralizing antibodies produced from the peptides of Table I and their homologues.

The protein products generated by the endogenous retroviral sequences or produced in parallel may be advantageously characterized by micro-methods of analysis and quantification of peptides and proteins: HPLC/FPLC or equivalent, capillary electrophoresis or equivalent, microsequencing techniques (Edman method or equivalent, mass spectrometry and the like).

The subject of the invention is also antibodies directed against one or more of the peptides described above and their use either for carrying out a method, in particular a differential method, of *in vitro* detection of the presence of such a sequence in an individual, or for the preparation of a composition capable of being used in serotherapy in neuropathological conditions with an autoimmune component.

Said antibodies are advantageously polyclonal or monoclonal antibodies obtained by an immunological reaction from a human, mammalian or avian organism or other species toward the proteins, as defined above.

The subject of the present invention is a method for the differential immunological screening of normal or pathological human endogenous retroviral sequences of the HERV-7q family, characterized in that it comprises bringing a biological sample into contact with an antibody according to the invention, the reading of the result being visualized by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

By way of illustration, such an *in vitro* diagnostic method according to the invention comprises bringing a biological sample collected from a patient into contact with antibodies according to the invention and detecting with the aid of any appropriate method, in particular with the aid of labeled anti-immunoglobulins, the immunological complexes formed between the proteins produced normally or pathologically and the antibodies.

Monoclonal or polyclonal antibodies, produced from antigens corresponding to synthetic peptides, or recombinant polypeptide or proteins make it possible to monitor the expression of the peptides or proteins produced normally or pathologically. The analysis is preferably carried out by ELISA or equivalent, Western blotting or equivalent, or by immunohistochemistry.

The peptides or proteins, derived from the endogenous retroviral sequences or whose expression is associated with the expression of these endogenous retroviral sequences, are tested for and identified.

The subject of the present invention is also a method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences according to the invention.

The subject of the present invention is also the application of the nucleic sequences or of the protein sequences according to the invention to the diagnosis of, to the prognosis of, to the evaluation of genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part of the nucleic sequences according to the invention and related endogenous or exogenous forms are involved.

The subject of the present invention is also hybrid nucleic sequences, characterized in that they comprise nucleic sequences or motifs according to the invention, combined with sequences or motifs of endogenous origin or of exogenous origin or induced exogenously.

The subject of the present invention is, in addition, a recombinant cloning or expression vector, characterized in that it comprises a nucleic sequence in accordance with the invention.

Therapeutic strategies may be envisaged by using some of the nucleic sequences contained in HERV-7q and the sequences of the same family or deduced

polypeptide structures or by the use of peptides or proteins, or of specific antibodies.

In accordance with the invention, all or part of the endogenous retroviral nucleic sequences of the HERV-7q type may be used for use as a vector or as vector elements for therapeutic use, in particular the LTR sequences and the *gag* region (SEQ ID NO: 2, 21 and 22).

The advantage of such sequences lies in the safety of the vector thus formed, in the possibility of a targeted specific insertion in a well-defined region by a strategy similar to homologous recombination, in cellular targeting, which is optionally transient in the case of a placental expression in women. Another aspect relates to the possibility of combining with the genes of interest the biologically active retroviral motifs (immunomodulatory peptides, as represented in the sequences SEQ ID NO: 68-118, below, fusogenic peptide and the like).

The subject of the present invention is also transgenic animals, characterized in that they comprise all or part of a sequence of the HERV-7q type (SEQ ID NO: 1-22 and 61).

Table II below establishes the correspondences between the sequence numbers as they appear in the sequence listing and the name of the various sequences.

TABLE II

SEQ ID NO:	DESIGNATION
1	Nucleic acid: 7 env
2	Nucleic acid: gag
3	Nucleic acid: HERV-7q
4	Nucleic acid: HE2
5	Nucleic acid: HE3
6	Nucleic acid: HG3
7	Nucleic acid: HE4
8	Nucleic acid: HE5
9	Nucleic acid: HE6
10	Nucleic acid: HG6
11	Nucleic acid: HE7
12	Nucleic acid: HE8
13	Nucleic acid: HG8
14	Nucleic acid: HE9
15	Nucleic acid: HE10
16	Nucleic acid: HE11
17	Nucleic acid: HG11
18	Nucleic acid: HE12
19	Nucleic acid: HG12
20	Nucleic acid: R1
21	Nucleic acid: RIF
22	Nucleic acid + deduced env protein: HERV-7q
23	Fragment of deduced env protein according to SEQ ID NO: 22
24	Fragment of deduced env protein according to SEQ ID NO: 22
25	Fragment of deduced env protein according to SEQ ID NO: 22
26	Protein: enverin
27	Fragment of deduced env protein according to SEQ ID NO: 22
28	Nucleic acid + protein deduced from gag: HERV-7q
29	Fragment of deduced gag protein according to SEQ ID NO: 28
30	Fragment of deduced gag protein according to SEQ ID NO: 28
31	Fragment of deduced gag protein according to SEQ ID NO: 28
32	Fragment of deduced gag protein according to SEQ ID NO: 28
33	Fragment of deduced gag protein according to SEQ ID NO: 28
34	Fragment of deduced gag protein according to SEQ ID NO: 28
35	env protein: reading frame 1
36	gag protein
37	Nucleic acid: G1F (primer)
38	Nucleic acid: G1R (primer)
39	Nucleic acid: G2F (primer)
40	Nucleic acid: G2R (primer)
41	Nucleic acid: G4F (primer)
42	Nucleic acid: G3F (primer)
43	Nucleic acid: G4R (primer)
44	Nucleic acid: G5R (primer)
45	Nucleic acid: E1F (primer)
46	Nucleic acid: E1R (primer)
47	Nucleic acid: E2F (primer)
48	Nucleic acid: E2R (primer)
49	Nucleic acid: E3F (primer)
50	Nucleic acid: E3R (primer)
51	Nucleic acid: E4F (primer)

SEQ ID NO:	DESIGNATION
52	Nucleic acid: E4R (primer)
53	Nucleic acid: E5F (primer)
54	Nucleic acid: E6F (primer)
55	Nucleic acid: E5R (primer)
56	Nucleic acid: ExF (primer)
57	Nucleic acid: ExR (primer)
58	Protein gag
59	Nucleic acid: Sequence A (insertion sequence)
60	Nucleic acid: Sequence B (insertion sequence)
61	Nucleic acid: HE13
62	Nucleic acid: RH7
63	Nucleic acid: RAM75
64	Nucleic acid: RAV73
65	Nucleic acid: RBP3
66	Nucleic acid: HI3
67	Nucleic acid: LTX
68	Peptide Table I
69	Peptide Table I
70	Peptide Table I
71	Peptide Table I
72	Peptide Table I
73	Peptide Table I
74	Peptide Table I
75	Peptide Table I
76	Peptide Table I
77	Peptide Table I
78	Peptide Table I
79	Peptide Table I
80	Peptide Table I
81	Peptide Table I
82	Peptide Table I
83	Peptide Table I
84	Peptide Table I
85	Peptide Table I
86	Peptide Table I
87	Peptide Table I
88	Peptide Table I
89	Peptide Table I
90	Peptide Table I
91	Peptide Table I
92	Peptide Table I
93	Peptide Table I
94	Peptide Table I
95	Peptide Table I
96	Peptide Table I
97	Peptide Table I
98	Peptide Table I
99	Peptide Table I
100	Peptide Table I
101	Peptide Table I
102	Peptide Table I
103	Peptide Table I
104	Peptide Table I
105	Peptide Table I

SEQ ID NO:	DESIGNATION
106	Peptide Table I
107	Peptide Table I
108	Peptide Table I
109	Peptide Table I
110	Peptide Table I
111	Peptide Table I
112	Peptide Table I
113	Peptide Table I
114	Peptide Table I
115	Peptide Table I
116	Peptide Table I
117	Peptide Table I
118	Peptide Table I
119	Nucleic acid: BLIMP-1
120	Peptide: CKH
121	Nucleic acid: F645 (primer)
122	Nucleic acid: PS5D (primer)

In addition to the preceding arrangements, the invention also comprises other arrangements which will emerge from the description which follows, which refers to exemplary embodiments of the method which is the subject of the present invention as well as to the appended drawings, in which:

- Figure 1. Human nucleic sequence HERV-7q, whose analysis and treatment make it possible to characterize a novel endogenous retroviral structure. The repeat nucleic regions of type R1 and R2 and the *gag, pol* and *env* domains are underlined. The *gag* and *env* type domains are in italics. The region homologous to a noncoding 3′ portion of Rab7 is double underlined.

- Figure 2. Map of the human endogenous retroviral region HERV-7q. The upper part of the figure corresponds to an anonymous region of the human genome situated on the long arm of chromosome 7. The repeat domains (1), *gag* (2), *pol* (3) and *env* (4) of HERV-7q can be identified. The C-terminal *env* region (4.3) is prolonged upstream in the form of a long open reading frame (4.2). The domain 4.1 corresponds to the N-terminal region of the *env* domain.

- Figure 3. Comparison of the repeat nucleic sequences situated at the boundaries of HERV-7q. The 5′

(top) and 3′ (bottom) repeat nucleic regions are compared and the identical bases are indicated by two dots.

- Figure 4. Deduced sequence having an open reading frame in the env-type domain of HERV-7q according to the longest open reading frame rule.

- Figure 5. Sequences around the CKS-17 domain identified in various deduced *env* domains of the HERV-7q family and comparison with reference CKS-17 motifs.

1) HE2 - 2) HERV-7q - 3) GenBank accession No.: M85205 - 4) HE7 - 5) HE9 - 6) CKS-17; the peptide motif endowed with immunomodulatory properties is underlined - 7) gp20 of retrovirus type D (SRV-Pc).

- Figure 6. Possible deduced sequence of the *gag*-type domain identified in HERV-7q established according to the longest open reading frame rule. X and / correspond to a non-sense codon and to a reading frame shift, respectively. The underlined sequence corresponds to the beginning of the *pol* domain.

- Figure 7. Comparison of the nucleic regions covering the *gag* region of HERV-7q (top) and HERV-TcR (bottom) and their flanking regions. The identical bases are specified by two dots.

- Figure 8. Example of nucleic alignments of the *env*-type domain of HERV-7q with similar *env*-type domains present in human endogenous retroviral sequences of the same family. The non-sense codons are underlined: 1) HERV-7q - 2) HE2 03) HE3 - 04) HE4.

- Figure 9. Nucleic alignments between the *gag* domain of HERV-7q and the corresponding domains belonging to the same family. Comparison with fragments of *gag* domains isolated from infectious retroviral agents. Sequences of infectious retroviral origin: EMBL database accession No.: 1) A60168 - 2) A60201 - 3) A60200 - 4) A60171. Human endogenous retroviral sequences: 5) HERV-7q - 6) HG11 - 7) HG3. The figures indicated in the endogenous sequences correspond to the number of nucleotides inserted in order to optimize the

alignment with the *gag*-type sequences identified in retroviruses of infectious origin.

- Figure 10. Alignment of a deduced *gag* protein motif (top) belonging to an infectious retrovirus (EMBL accession No.: A60200) with the deduced *gag* protein motif (bottom) identified in HERV-7q. The non-sense codons are in bold and underlined. The identical amino acids are specified by 2 dashes. One dash indicates a deletion or a homologous amino acid.

- Figure 11. Alignment of an *env* motif (top) belonging to an infectious retrovirus (EMBL accession No.: A60170) with the *env* motif (bottom) identified in HERV-7q. The homologous nucleotides are specified by two dots and the deletions by a dash.

- Figure 12. Comparison between the *env* domain of HERV-7q (top) and the *env* domain of HERV-9 (bottom). The 66% homology is limited to the 3′ region of the *env* domain of HERV-7q and HERV-9, respectively between nucleotides 8976 nt and 9500 nt of HERV-7q and nucleotides 2898 nt and 3465 nt of HERV-9 (GenBank accession No.: X57147). Numerous insertions/deletions are also observed.

- Figure 13. Homology between a portion of the sequence of the transcript encoding RH7 (top, SEQ ID NO: 62) and an RGH2 motif (bottom - GenBank accession No.: D11018).

-Figure 14. Identification of the sequence of the transcript encoding RAM75 (SEQ ID NO: 63), corresponding to the gene for an ATPase of PEX1 type. The coding exons are underlined. The initiation and non-sense codons as well as the putative poly-adenylation sites are in bold and underlined. The region in italics corresponds to the beginning of the endogenous retroviral sequence RH7.

- Figure 15. Sequence of the transcript encoding RAV73 (SEQ ID NO: 64), situated at 0.7 kb downstream of HERV-7q; the nucleic sequences capable of encoding one or more polypeptides are underlined.

- Figure 16. Comparison between the 3′ LTR sequence (top) of HERV-7q and the intron sequence LTX (SEQ ID NO: 67), situated in the FMR2 gene, associated with fragile X (bottom).

- Figure 17. Detection of modifications on the nucleotide sequence (ID NO: 3), in patients suffering from MS. The modified bases, in at least one patient, are underlined. The primers used are in italics (sequences SEQ ID NO: 121 and 122). The initiation ATG and the non-sense codon are in bold.

- Figure 18. The *env* coding portion of the HERV-7q sequence (sequence ID NO: 3), with 3 reading frames.

- Figures 19, 20, 21. Separate presentation of the env protein according to the 3 reading frames.

- Figure 22. Nucleic sequence containing the retroviral sequence RH7 situated in 5′ of the HERV-7q sequence. The sequence in italics corresponds to the beginning of the HERV-7q sequence. The RH7 sequence is underlined. Two putative polyadenylation sites are in bold.

- Figure 23. Sequence of the transcript encoding RBP3 containing nucleotide motifs identified in the nucleic sequence encoding the Blimp-1 gene.

- Figure 24. Sequence of the transcript encoding APS.

- Figure 25. Sequence of the transcript encoding Blimp-1; the coding portion is underlined; the initiation and termination codons are in bold.

- Figure 26. Sequence of the transcript encoding FMR2. The coding portion is underlined. The initiation and non-sense codons are in bold.

It should be clearly understood, however, that these examples are given solely by way of illustration of the subject of the invention and do not in any manner constitute a limitation thereto.

<u>EXAMPLE 1</u>: Detection, by gene amplification, of a nucleic sequence belonging to a domain of the *gag* or *env* type according to the invention, in a genomic DNA sample of human or mammalian origin

The gene amplification is carried out using genomic DNA isolated from blood. An anticoagulant treatment is carried out with 1 ml of a citrate solution (per liter: 4.8 g of citric acid, 13.2 g of sodium citrate, 14.7 g of glucose) per 6 ml of fresh blood. After centrifugation of 20 ml of blood for 15 min at 130 000 g, the supernatant is removed and the fraction enriched with white blood cells is transferred into a new tube and then recentrifuged under the same conditions as above. The fraction enriched with white blood cells is resuspended in an extraction buffer (10 nM Tris-HCl, 0.1 M EDTA, 20 µg/ml of pancreatic RNAse treated so as to eliminate the DNAses, 0.5% SDS, pH 8.0), and then incubated for 1 hour at 37°C. Proteinase K is added at a final concentration of 100 µg/ml. The suspension of lyzed cells is incubated at 50°C for 3 hours, with occasional stirring, and then treated with an equal volume of phenol equilibrated with 0.5 M Tris-HCl, pH 8.0. The emulsion formed is placed on a wheel for one hour and then centrifuged at 5 000 g for 15 min at room temperature. The aqueous solution is treated and deproteinized by a triple phenol extraction in order to obtain a level of purification corresponding to an absorbance A260/A280 final ratio greater than 1.75. The aqueous fraction is precipitated with 0.2 vol. of 10 M sodium acetate and 2 vol. of ethanol. The DNA is then either collected with the tip of a bent Pasteur pipette, or centrifuged at 5 000 g for 5 min at room temperature. The DNA or the DNA pellet is washed twice with 70% ethanol and then taken up in 1 ml of TE, pH 8.0 so as to be eluted, with gentle stirring, for 12 to 24 hours.

Oligonucleotides specific for the endogenous sequences described according to the invention are chosen in order to amplify the *gag* or *env* region of the

endogenous retroviral regions described according to the invention. The genomic DNA studied is obtained from patients having pathological conditions such as multiple sclerosis and from individuals reputed to be healthy.

The thermostable DNA polymerases used were chosen for their high accuracy during the amplification process, such as Vent DNA polymerase (Biolabs) and the like, and are used according to the conditions recommended by the supplier.

The amplification strategy uses, depending on the case, a simple PCR, or a nested or seminested PCR.

Oligonucleotides used to amplify the *gag* region:

- primer G1F, sense, located in the region upstream of the *gag* domain of *HERV*-7q (SEQ ID NO: 37),
- primer G1R, antisense, located in the 3′ terminal region of the *gag* domain (SEQ ID NO: 38).

The fragment of 1505 nt amplified by the pair G1F-G1R; 1505 nt is used to generate the probes capable of hybridizing the various PCR amplification products.

- primer G2F, sense nested (SEQ ID NO: 39),
- primer G2R, antisense nested (SEQ ID NO: 40),
- primer G4F, sense nested (SEQ ID NO: 41),
- primer G3F, sense nested (SEQ ID NO: 42),
- primer G4R, antisense nested (SEQ ID NO: 43),
- primer G5R, antisense nested (SEQ ID NO: 44).

Oligonucleotides used to amplify the *env* region of HERV-7q:

- primer E1F, sense (SEQ ID NO: 45),
- primer E1R, antisense (SEQ ID NO: 46).

The fragment of 2529 nt amplified by the pair of primers E1F-E1R is used to generate the probes capable of hybridizing the various PCR amplification products.

- primer E2F, sense (SEQ ID NO: 47),
- primer E2R, antisense (SEQ ID NO: 48),
- primer E3F, sense (SEQ ID NO: 49),
- primer E3R, antisense (SEQ ID NO: 50),

- primer E4F, sense (SEQ ID NO: 51),
- primer E4R, antisense (SEQ ID NO: 52),
- primer E5F, sense (SEQ ID NO: 53),
- primer E6F, sense (SEQ ID NO: 54),
- primer E5R (SEQ ID NO: 55),
- primer ExF (SEQ ID NO: 56),
- primer ExR (SEQ ID NO: 57).

The PCR is carried out using 50 to 200 ng of genomic DNA. The PCR conditions are those recommended by the supplier. The amplification cycle conditions are carried out in 50 μl: denaturation of 94°C for 1 min, hybridization of 70°C for 1 min, and extension at 72°C for 1 to 2 min, depending on the amplified fragments. After 35 cycles, a terminal reaction is carried out at 72°C for 10 min. Automated sequencing of the amplified samples is carried out with the aid of an Applied Biosystems type ABI 377 sequencer or another comparable model, according to the protocols provided by the manufacturer.

In the case of a nested or seminested PCR, the same experimental conditions are used, the only difference being that the genomic DNA sequence is replaced with 5 to 10 μl of the amplification product derived from the first PCR.

Two independent amplifications are carried out using the same sample. A control reaction is carried out by replacing the DNA sample with water in order to detect possible contaminants.

<u>EXAMPLE 2</u>: Detection, by gene amplification, of a nucleic sequence according to the invention in a biological sample of genomic DNA collected from patients having an existing candidate pathological condition or suspected of having this pathological condition

The amplification protocol is the same as in Example 1, apart from the origin of the sample which is obtained from patients having a candidate pathological condition. A genomic DNA sample reputed to be normal is

systematically integrated into the set of amplified pathological samples and then analyzed.

The PCR products are separated on a 1.5% agarose gel and then transferred in the presence of 0.4 N sodium hydroxide on a charged nylon membrane. Hybridization is carried out with a specific probe corresponding to the PCR fragments amplified either with the pair G1F-G1R or the pair E1F-E1R. The probe is labeled by incorporating dUTP-digoxygenin according to the supplier's protocol (Boehringer Mannheim). The hybridization is carried out in a hybridization buffer (5XSSC, 50% formamide, 0.1% lauroylsarcosine, 0.02% SDS, 2% blocking reagent Boehringer) overnight at 42°C. The Southern is washed for twice 5 min at room temperature in a 2XSSC solution containing 0.1% SDS. Next, a high stringency wash is carried out twice for 15 min at 55°C in a 0.1XSSC solution containing 0.1% SDS. The hybridization is visualized according to the supplier's protocol (Boehringer Mannheim), in the presence of a chemiluminescent substrate for alkaline phosphatase, of the CSPD or CDP-STAR type. The filter is visualized after a 15 min exposure at 60°C.

SSCP (*single strand conformation polymorphism*) analysis makes it possible to detect discrete modifications of the sequence of the fragments amplified by PCR. The PCR is carried out in the presence of dCTP labeled with ^{32}P. The sample to be analyzed is denatured at 95°C for 10 min in the presence of loading buffer, and then immediately loaded onto a 10% polyacrylamide gel containing 7.5% glycerol. The migration is carried out at 4°C at 8-10 W. The gel is dried and then autoradiographed.

The PCR fragments likely to exhibit an alteration of their nucleotide sequence are sequenced according to Example 1.

Hybridization with the aid of a specific oligonucleotide (17 mers to 20 mers) corresponding to the modified nucleotide region makes it possible to identify the samples having an identical modification

(ASO method). Briefly, the southern is hybridized with an oligonucleotide which is distally labeled either with ^{32}P, or in the presence of digoxygenin (according to the Boehringer Mannheim protocol) and then washed under stringent conditions at 65°C in a 6XSSC solution containing 0.05% sodium pyrophosphate.

For example, an automated nucleotide sequencing was carried out on six PCR fragments obtained from 5 patients suffering from MS and a control reputed to be normal, and which were amplified using the primers F645: CTTCAAACAACAACCAGGAGG (SEQ ID NO: 121) (situated 26 nucleotides upstream of the initiation methionine of enverin) and PS5D: TTGGGGAGGTTGGCCGACGA (SEQ ID NO: 122) (situated 6 nucleotides downstream of the non-sense codon of enverin). Modifications of the sequence of enverin were observed on the DNA from some patients (Figure 17).

__EXAMPLE 3__: Detection of a protein according to the invention in a biological sample

- Preparation of a purified protein fraction of cerebrospinal fluid from patients suffering from MS

After a treatment at 56°C for 30 min and removal of the immunoglobulins on a G HiTrap protein column (Pharmacia), the equivalent of 10 ml of CSF is deposited on a DEAE Sepharose CL-6B column (Pharmacia). The elution is carried out in 20 mM Tris-HCl, pH 8.8, and a gradient from 0 to 0.4 M NaCl, and then the fraction is dialyzed twice against a phosphate-NaCl buffer (PBS). After concentration on Ultrafree-MC (Millipore), the fraction is deposited on a Superose 12 column (FPLC Pharmacia) and eluted in the presence of PBS. After separation by polyacrylamide-SDS gel electrophoresis and electrotransfer onto an Immobilon-P membrane (Millipore), the protein bands are subjected to controlled trypsin hydrolysis.

- Analysis of the protein fraction by mass spectrometry

The peptides digested in the presence of trypsin are analyzed by the MALDI-TOF method, which

allows the analysis of peptides present in a mixture (COTTRELL J.S., Pept. Res., 1997, 7, 115-124). The peptides characterized according to their mass are compared with the proteins and with the associated proteins according to the invention.

<u>EXAMPLE 4</u>: Detection of specific antibodies to the *env* domain of HERV-7q

The identification of a long open reading frame in the *env* sequence of HERV-7q made it possible to determine a deduced protein sequence SEQ ID NO: 22 and 35 and Figures 18-20 of a region of the said gene.

The protein sequences deduced from the sequences ID NO: 22, 35 and Figures 18-20 are positioned as follows with respect to Figure 1 or the sequence ID NO: 3:

SEQ ID NO: 22 (reading frame 1) and Figure 19: beginning of the coding sequence: position 7874, end of the coding sequence 1st nonsense codon (position 9493)

SEQ ID NO: 35: beginning of the coding sequence: position 7874, end of the coding sequence 1st nonsense codon (position 9493) (reading frame 1)

Figure 19: beginning of the coding sequence: position 6970, end of the coding sequence 1st nonsense codon (position 9493) (reading frame 1)

Figure 20: beginning of the coding sequence: position 6971, the end of the reading frame is shifted depending on the case by 1, 2 or 3 codons

Figure 21: beginning of the coding sequence: position 6972, the end of the reading frame is shifted depending on the case by 1, 2 or 3 codons

Various peptides corresponding to all or part of SEQ ID NO: 22 (see SEQ ID NO: 23-27 and 35) were synthesized by genetic engineering in order to test their antigenic specificity toward sera or tissues from patients suffering from MS, for example. Briefly, all or part of the env region of HERV-7q is subcloned into the vectors pQE30, 31 and 32. The vectors pQE30, 31 and 32 contain, in 5′ of the multiple cloning site, the consensus sequences for transcription (the strong T5

bacteriophage promoter, 2 operators of the lactose operon) and translation (one synthetic ribosome binding site). Likewise, pQE30, 31 and 32 possess, in 3', the phage 1 transcription terminator as well as a Stop codon for translation. The expression of the protein is carried out after transformation in *E. coli* M15. The plasmid pQE30, 31 and 32 possess, upstream of the multiple cloning site, the coding sequence for a succession of 6 histidines having affinity for nickel ions. This stretch allows the purification of the expressed chimeric protein by adsorption on a resin consisting of a chelating ligand, nitrotriacetic acid (NTA), charged with 4 nickel ions (NI-NTA resin, Qiagen).

The transformation is carried out by electroporation or treatment with calcium chloride. For example, an *E. coli* M15 colony is incubated in 100 ml of LB medium containing 250 μg of kanamycin, with stirring at 37°C until an OD^{600} of 0.5 is obtained. After centrifugation for 5 minutes at 2000 g at 4°C, the bacterial pellet is taken up in 30 ml of TFB1 solution (100 mM rubidium chloride, 50 mM manganese chloride, 30 mM potassium acetate, 10 mM $CaCl_2$, 15% glycerol, pH 5.8), at 4°C for 90 minutes. After a centrifugation of 5 minutes at 2000 g at 4°C, the bacterial pellet is taken up in 4 ml of TFB2 solution (10 mM rubidium chloride, 10 mM MOPS, 75 mM $CaCl_2$, 15% glycerol, pH 8). The cells may be kept at -70°C in aliquots of 500 ml. 20 μl of the ligation and 125 μl of competent cells are mixed and placed on ice for 20 minutes. After a heat shock of 42°C for 90 seconds, the cells are stirred for 90 minutes at 37°C in 500 ml of Psi-broth medium (LB medium supplemented with 4 mM $MgSO_4$, 10 mM potassium chloride). The transformed cells are plated on LB-agar dishes supplemented with 25 μg/ml of kanamycin and 100 μg/ml of ampicillin, and the dishes are incubated overnight at 37°C.

The potentially recombinant clones are subcultured in an orderly manner on a nylon filter

deposited on an LB-agar dish supplemented with 25 μg/ml of kanamycin and 100 μg/ml of ampicillin. After one night at 37°C, the recombinant clones are located by hybridization of the plasmid DNA with the nucleotide probe amplified by PCR with the pair of primers according to SEQ ID NO: 45 and SEQ ID NO: 46.

An independent colony containing the insert is inoculated at 20 ml of LB medium supplemented with 25 μg/ml of kanamycin and 100 μg/ml of ampicillin. After one night at 37°C, with stirring, 500 ml of the same medium are incubated at 1/50 with this preculture until an OD^{600} of 0.8 is obtained, and then 1 to 2 mM final of IPTG is added. After 5 hours, the cells are centrifuged for 20 minutes at 4 000 g.

A portion of the cellular pellet is taken up in 5 ml of sonification buffer (50 mM of sodium phosphate, pH 7.8, 300 mM NaCl) and then placed on ice. After rapid sonification, the cells are centrifuged for 20 minutes at 10 000 g. A portion of the cellular pellet is taken up in 10 ml of a 30 mM Tris/HCl-20% sucrose solution pH 8. The cells are incubated for 5 to 10 minutes, with stirring, after addition of 1 mM EDTA. After a centrifugation of 10 minutes at 8 000 g at 4°C, the pellet is taken up in 10 ml of 5 mM ice cold $MgSO_4$. After 10 minutes on the ice, with stirring, the cells are centrifuged for 10 minutes at 8 000 g at 4°C.

The pellet is taken up in 5 ml/g in buffer A (6 M GuHCl (guanidine hydrochloride), 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 8), 1 hour at room temperature. The lysate is centrifuged for 15 minutes at 10 000 g at 4°C, and the supernatant is supplemented with 8 ml of Ni-NTA resin, pre-equilibrated in buffer A. After 45 minutes at room temperature, the resin is poured into a column, washed with 10 times the column volume with buffer A and then with 5 times the column volume with buffer B (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 8). The column is washed with buffer C (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 6.3) until A280 is less than 0.01. The

recombinant protein is eluted with 10 to 20 ml of buffer D (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 5.9) and then with 10 to 20 ml of buffer E (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 4.5), and then with 20 ml of buffer F (6 M HCl, 0.2 M acetic acid). After SDS-PAGE analysis, the purified fraction(s) containing the chimeric protein allowed the production of antibodies in rabbits. The antibodies obtained are tested by Western blotting after visualization with a secondary antibody coupled to alkaline phosphatase.

Antibodies are obtained in the same manner, using peptides synthesized chemically according to the Merrifield technique (G. Barany and B. Merrifield, 1980, in *The peptides*, 2, 1-284, E. Gross and J. Meienhofer, Academic Press, New York).

The specific antibodies obtained are used for detection of the serum or tissue expression of all or part of the endogenous retroviral sequences according to the invention, in normal and pathological cases.

The proteins of serum or tissue origin are separated on acrylamide-SDS gel and then transferred onto a nitrocellulose filter with the aid of a Novablot 2117-2250 apparatus (LKB). The transfer is carried out on a Hybond C-extra sheet (Amersham) using a 100 mM CAPS buffer pH 11, methanol, water (V/V/V: 1/1/8) containing 1 mM $CaCl_2$. After a transfer of 1 hour at 0.8 mA/cm^2, the sheet is saturated for 1 hour at room temperature in PBS-0.5% gelatin. The sheet is brought into contact with the specific antibody at the concentration of 1/1 000 in PBS-0.25% gelatin. After 2 hours, the filter is washed 3 times 15 minutes in PBS-0.1% Tween-20, and then the filter is incubated for 30 minutes in the presence of a secondary antibody coupled to alkaline phosphatase (Promega), diluted 1/7 500 in PBS-0.25% gelatin. After three washes in PBS-0.1% Tween-20, the filter is equilibrated in a buffer (100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM $MgCl_2$). The visualization is carried out in the presence

of 45 μl of NBT at 75 mg/ml and 35 μl of BCIP at 50 mg/ml, per 10 ml of alkaline phosphatase buffer.

The chimeric proteins obtained by genetic engineering are also used for tests of biological activity, such as for example the test for biological activity of the CKS-17-type peptide identified in the *env* domain of HERV-7q (Figure 5).

<u>EXAMPLE 5</u>: Production of ribonucleic probes encoding the *env* sequences of HERV-7q

The PCR fragments obtained are subcloned into the plasmid PGEM 4Z (Promega) which possesses on either side of its multiple cloning site, promoter sequences for the SP6 and T7 RNA polymerases.

The method of competence used is electroporation. The plasmid and the PCR fragment are hybridized in a ratio of 50 ng of vector (SmaI cleavage) to 100 ng of PCR fragment (made blunt ended by treatment with the Klenow fragment of DNA polymerase). The incubation takes place overnight at 22°C in ligation buffer (66 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 1 mM dithioerythritol, 1 mM ATP) in the presence of 1 u of T4 DNA ligase and is then stopped by denaturation for 10 minutes at 65°C. In parallel, the *E. coli* JM 105 strain is inoculated overnight at 37°C in LB medium. This preculture is diluted 1/500 and placed at 37°C until an OD^{600} equal to 1 is obtained. For the remainder of the procedure, the cells will always be stored at cold temperature. After centrifugation for 5 minutes at 3 500 g at 4°C, the cellular pellet is resuspended in 1/4 vol. of ultra-pure ice-cold water. This step is repeated 5 to 6 times. The pellet is then resuspended in 1/4 000 vol. of water; 10% of sterile glycerol is added, allowing preservation of the electrocompetent cells, in aliquots of 10 μl at 20°C. 1 μl of the ligation is added to 50 μl of electrocompetent cells; the mixture is subjected to an electrical discharge of 12.5 kV/cm, applied for 5.8 ms. The cells are rapidly resuspended in the SOC medium, incubated for 1 hour at 37°C and

then plated in the presence of 2% X-Gal in dimethylformamide, and 10 mM IPTG, on an LB-agar dish supplemented with ampicillin (100 μg/ml). After one night at 37°C, the potentially recombinant white clones are subcultured in an orderly manner on an LB/ampicillin dish and in parallel on a nylon filter deposited on an LB/ampicillin dish. These two dishes are incubated overnight at 37°C. The recombinant clones are then located by hybridization with a nucleic probe amplified by PCR with the pair or primers according to SEQ ID NO: 45 and SEQ ID NO: 46 and labeled with digoxygenin.

The recombinant clones are cultured in 50 ml of LB/ampicillin medium (100 μg/ml), with stirring, overnight at 37°C. After centrifugation at 3 500 g for 15 minutes at 4°C, the bacterial pellet is taken up in 4 ml of P1 buffer (50 mM Tris-HCl, 10 mM EDTA, 400 μg/ml RNase A, pH 8) and 4 ml of P2 buffer (200 mM NaOH, 1% SDS). The medium is incubated at room temperature for 5 minutes. After addition of 4 ml of P3 buffer (2.55 M potassium acetate, pH 4.8), the mixture is centrifuged at 12 000 g for 30 minutes at 4°C. This supernatant is applied to a Qiagen type 100 column, pre-equilibrated with 2 ml of QBT buffer (750 mM NaCl, 50 mM MOPS, 15% ethanol, pH 7), the column is washed with twice 4 ml of QC buffer (1 M NaCl, 50 mM MOPS, 15% ethanol, pH 7) and the DNA is eluted with 2 ml of QF buffer (1.2 M NaCl, 50 mM MPOS, 15% ethanol, pH 8). The DNA is precipitated with 0.8 vol. of isopropanol and centrifuged at 12 000 g at 4°C for 30 minutes. The pellet is washed with 70% ice-cold ethanol and then the plasmid DNA is taken up in twice 150 μl of TE buffer.

The ribonucleic probes are used as specific probes, in particular for the detection of the transcripts expressed by the endogenous retroviral sequences according to the invention.

EXAMPLE 6: Construction of a transgenic mouse containing all or part of the gene for enverin

A transgenic mouse containing all or part of the HERV-7q sequence (SEQ ID NO: 3) is constructed so as to identify the sequences responsible for the tissue specificity, and to evaluate the role of all or part of the endogenous retroviral motifs of the HERV-7q type, in particular all or part of the peptide motifs of enverin. The microinjection technique used refers to the conventional technique (Hogan et al., (1994), Manipulating the mouse embryo, Cold Spring Harbor, Cold Spring Harbor Laboratory Press) or to its equivalents. Forms identical to the normal human molecule of motifs of the HERV-7q type, including enverin, or forms which are mutated, deleted, having insertions, or truncated are tested in order to determine the motifs which are critical both from the normal and pathological point of view, and more particularly during fetal development and during tumor processes.

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As is evident from the above, the invention is not at all limited to its embodiments, implementations and applications which have just been described more explicitly; it embraces on the contrary all the variants which may occur to a specialist in this field, without departing from the framework or scope of the present invention.

CLAIMS

1. A purified nucleic acid fragment, characterized in that it comprises all or part of a sequence encoding a human endogenous retroviral sequence, which has at least *env*-type retroviral motifs, corresponding to the sequence SEQ ID NO: 1 or to a sequence exhibiting a level of homology with the said sequence SEQ ID NO: 1 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains.

2. The nucleic acid fragment as claimed in claim 1, characterized in that it has retroviral motifs corresponding to an *env* domain and corresponding to the sequence SEQ ID NO: 1 and retroviral motifs corresponding to a *gag* domain and corresponding to the sequence SEQ ID NO: 2 or to a sequence exhibiting a level of homology greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains and a level of homology greater than or equal to 90% on more than 700 nucleotides or greater than or equal to 70% on more than 1 200 nucleotides for the *gag*-type domains, the said motifs having no insertion or deletion of more than 200 nucleotides.

3. A nucleic acid fragment, characterized in that it comprises a segment of a sequence as claimed in claim 1 or claim 2 and in particular the sequence SEQ ID NO: 3-22, 28 and 61, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences as well as fragments derived from the coding regions of the preceding sequences corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

4. Transcripts, characterized in that they are generated from the sequences as claimed in any one of claims 1 to 3.

5. A diagnostic reagent for the differential detection of complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label.

6. The reagent as claimed in claim 5, characterized in that it is chosen from the regions situated between nucleotides 3065 and 4390, nucleotides 6965 and 9550 or nucleotides 2502-2865 of SEQ ID NO: 3.

7. The reagent as claimed in claim 5, characterized in that it is selected from the sequences SEQ ID NO: 37-57, 59-60 and 121-122 and in that it is capable of being used as a primer.

8. The reagent as claimed in claim 5, characterized in that it is selected from the following sequences:

- a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),
- a fragment of 2529 nt amplified by the pair of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R),
- a fragment of 182 nucleotides, repeated twice, situated upstream of the *gag* domain at positions 2502-2611/2613-2865,

and in that it is capable of being used as a probe.

9. The reagent as claimed in claim 5, characterized in that it is chosen from the group consisting of the fragments encoding or not encoding all or part of enverin, in particular the fragments comprising at least 14 nucleotides and more particularly the fragments encoding the C-terminal portion of enverin, either from the amino acid 291, or from the amino acid 321, starting from the codon encoding the first methionine.

10. A method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the *env* or *env* and *gag* type, their normal or pathological variants, by hybridization and/or gene amplification, carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analyzed is brought into contact with at least one probe as claimed in claim 5, claim 6 or claim 8, and

(b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

11. The method of detection as claimed in claim 10, characterized in that it comprises:

* prior to step (a):

. a step of preparing the relevant biological tissue or fluid,

. a step of extracting the nucleic acid to be detected, and

. at least one gene amplification cycle carried out with the aid of at least one reagent as claimed in any one of claims 5 to 7, and

* subsequent to step (b):

. a step of comparing the nucleic sequences obtained in the said biological sample with the human endogenous retroviral sequences as claimed in any one of claims 1 to 3, by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a

deletion or a single mutation between the various sequences compared.

12. A method of detecting the transcripts as claimed in claim 4, characterized in that it comprises:

- collecting messenger RNAs obtained from control biological samples and from a similar sample collected from patients, and

- the qualitative and/or quantitative analysis of the said mRNAs by *in situ* hybridization, by dot-blot, Northern blotting, RNAse mapping or RT-PCR, with the aid of a diagnostic reagent as claimed in any one of claims 5 to 9.

13. Chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence selected from the group consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, associated with an endogenous retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides as claimed in claims 1 to 4.

14. A method for the detection and/or evaluation of an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, as claimed in any one of claims 1 to 9, characterized in that it comprises:

- depositing on an appropriate support, cDNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or from specific oligonucleotide sequences, the said

DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/ deregulation of motifs belonging to the said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as claimed in claim 13,

- the hybridization of the said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and

- the detection of the hybrids formed.

15. The method as claimed in claim 14, characterized in that the said transcript or cDNA is selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

16. The method as claimed in claim 14 or claim 15, characterized in that the said support comprises, in addition, any endogenous or exogenous retroviral sequence.

17. The kit for the detection and/or evaluation of an autoimmune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in

addition to the buffers necessary for carrying out a method according to any one of claims 14 to 16:

- diagnostic reagents A as claimed in any one of claims 5 to 9, and

- reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/de-regulation or alteration is associated with the normal or pathological expression or with the regulation/de-regulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

18. The kit as claimed in claim 17, characterized in that said reagents B are selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

19. Translational products, characterized in that they are encoded by a nucleotide sequence as claimed in any one of claims 1 to 4.

20. A peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO: 1-22, 28 and 61 as claimed in any one of claims 1 to 4.

21. The peptide as claimed in claim 20, characterized in that it includes the derived peptides comprising between 5 and 540 amino acids and in particular a fragment of 538 amino acids, starting at the first methionine of the sequence SEQ ID NO: 26 (enverin).

22. The peptide as claimed in claim 20 or claim 21, characterized in that it is selected from the group consisting of:

. the sequences SEQ ID NO: 23-36;

. the sequence SEQ ID NO: 58;

. a C-terminal fragment of the sequence SEQ ID NO: 26, either from the amino acid 291, or from the amino acid 321, starting from the first methionine of the sequence SEQ ID NO: 26;

. a peptide of the CKS-17/CKS-25 type present in one of the sequences SEQ ID NO: 23-36 or 58; and

. the peptides having affinity with one of the haplotypes of the class I or class II HLA system and in particular the fragments 399-471, 244-271 of enverin, as well as the peptides having the sequence SEQ ID NO: 68-118, in accordance with Table I.

23. The peptide as claimed in any one of claims 20 to 22, characterized in that it is obtained from nucleic sequences as claimed in any one of claims 1 to 4, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).

24. Immunogenic or vaccine compositions for protecting against autoimmune diseases, in particular in at motif selected risk subjects, characterized in that it comprises at least one peptide comprising at least one motif of the CKS type and/or at least one motif selected from the group consisting of the peptides having affinity with one of the haplotypes of the class I or class II HLA system and at least one pharmaceutically acceptable vehicle.

25. The composition as claimed in claim 24, characterized in that said peptide having affinity with one of the haplotypes of the class I or class II HLA system is selected from the group consisting of the peptides as defined in Table I.

26. The composition as claimed in claim 24 or claim 25, characterized in that said peptide has the sequence SEQ ID NO: 120.

27. An antibody, characterized in that it is directed against one or more of the peptides as claimed in any one of claims 20 to 23.

28. A pharmaceutical composition, characterized in that it comprises neutralizing antibodies produced from the peptides of Table I (SEQ ID NO: 68-118) and their homologues.

29. A method for the differential immunological screening of normal or pathological human endogenous retroviral sequences of the HERV-7q family, characterized in that it comprises bringing a biological sample into contact with an antibody as claimed in claim 27, the reading of the result being visualized by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

30. A method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences as claimed in any one of claims 19 to 23.

31. An application of the sequences as claimed in any one of claims 1 to 9, 13, 14 or 19 to 23 to the diagnosis of, to the prognosis of, to the evaluation of genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part of the sequences as claimed in to any one of claims 1 to 5 and related endogenous or exogenous forms are involved.

32. Hybrid nucleic sequences, characterized in that they comprise sequences or motifs as claimed in any one of claims 1 to 9, combined with sequences or motifs of

endogenous origin or of exogenous origin or induced exogenously.

33. A recombinant cloning or expression vector, characterized in that it comprises a nucleic sequence as claimed in any one of claims 1 to 4.

34. An immunogenic or vaccine composition, characterized in that it comprises a vector including at least one nucleic sequence encoding a peptide as defined in Table I, optionally combined with a sequence encoding a motif of the CKS-17 type.

35. A gene therapy vector, characterized in that it comprises all or part of the endogenous retroviral nucleic sequences of the HERV-7q type as claimed in any one of claims 1 to 4.

36. The vector as claimed in claim 35, characterized in that said sequences are selected from the group consisting of the sequences SEQ ID NO: 2, 20 and 21.

37. Transgenic animals, characterized in that they comprise all or part of a sequence of the HERV-7q type (SEQ ID NO: 1-22, 28 and 61).

Abstract

The invention concerns a novel nucleic sequence and deduced protein sequence family with whole or partial human endogenous retroviral motifs. The invention also concerns the detection and/or the use of said nucleic sequences and said corresponding protein sequences or fragments of said sequences, for diagnostic, prophylactic and therapeutic uses, in particular for neuropathological conditions with autoimmune constituent such as multiple sclerosis. Said purified nucleic acid sequences comprise all or part of a sequence coding for a human endogenous retroviral sequence having at least *eny*-type retroviral motifs, corresponding to the sequence SEQ ID NO:1 or to a sequence having a homology level with said sequence SEQ ID NO:1 not less than 80% of more than 190 nucleotides or not less than 70% on more than 600 nucleotides for *env*-type domains. The invention further concerns the use of the flanking or adjacent sequence of said sequences and controlled by the latter, as diagnostic reagents.

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CCCTGGGGCGGGCTTCCTTTCTGGGATGAGGGCAAAACGCCTGGAGATACAGCAATTATCTTGCAACTGAG 71
AGACAGGACTAGCTGGATTTCCTAGGCCGACTAAGAATCCCTAAGCCTAGCTGGGAAGGTGACCACGTCCAC 143
CTTTAAACACGGGGCTTGCAACTTAGCTCACACCTGACCAATCAGAGAGCTCACTAAAATGCTAATTAGGCA 215
AAGACAGGAGGTAAAGAAATAGCCAATCATCTATTGCCTGAGAGCACAGCAGGAGGGACAACAATCGGGATA 287 repeat
TAAACCCAGGCATTCGAGCTGGCAACAGCAGCCCCCCTTTGGGTCCCTTCCCTTTGTATGGGAGCTGTTTTC 359 region
ATGCTATTTCACTCTATTAAATCTTGCAACTGCACTCTTCTGGTCCATGTTTCTTACGGCTCGAGCTGAGCT 431
TTTGCTCACCGTCCACCACTGCTGTTTGCCACCACCGCAGACCTGCCGCTGACTCCCATCCCTCTGGATCCT 503 R1
GCAGGGTGTCCGCTGTGCTCCTGATCCAGCGAGGCGCCCATTGCCGCTCCCAATTGGGCTAAAGGCTTGCCA 575
TTGTTCCTGCACGGCTAAGTGCCTGGGTTTGTTCTAATTGAGCTGAACACTAGTCACTGGGTTCCATGGTTC 647
TCTTCTGTGACCCACGGCTTCTAATAGAACTATAACACTTACCACATGGCCCAAGATTCCATTCCTTGGAAT 719
CCGTGAGGCCAAGAACTCCAGGTCAGAGAATACGAGGCTTGCCACCATCTTGGAAGCGGCCTGCTACCATCT 791
TGGAAGTGGTTCACCACCATCTTGGGAGCTCTGTGAGCAAGGACCCCCCGGTAACATTTTGGCAACCACGAA 863
CGGACATCCAAAGTGGTGAGTAATATTGGACCACTTTCACTTGCTATTCTGTCCTATCCTTCCTTAGAATTG 935
GAGGAAAATACCGGGCACTTGTCGGCCAGTTAAAAACGATTAGTGTGGCCACCGGACTTAAGACTCAGGTGT 1007
GAGGCTATCTGGGGAAGGGCTTTCTAACAACCCCCAACCCTTCTGGGTTGGGGACTTGGTTTGCCTCAAGCC 1079
AGCTTCCACTTTCAGTTTTCTTGGGGAAGCCGAGGGCCGACTAGAGGCAGAAAGCTGTCGTCCTGAACTCCC 1151
GGCAGTAGCCGGTTGAGATCATGGTGTAGCCAGAAGTCTCAACAGTCGCCCATGCATGCACCCCTATCTTTC 1223
CTTCTGACCCATACCTCCTGGGTCCCAACCACAACTTTCTTCAAAGTGTAGCCCCAAAATTCTCCTTACCTC 1295
TGAATATACTTCCTCTGATCCCTGCCTCCTAGGTACTATTGGTTCAGACTTCCATTTCCTCTAGCAAGTTGT 1367
ATCTCCAAAGGGATCTAAGGAAGCTCTGCGCTGCGTCCTTAGGCACCTAGGCTATAACCCAGGGAGTCTTAT 1439
CCCTGGTGTCCCTCCCAATTTAGGCATACAGCTCTTGACATGGGCAGTTATGTAGGACCCACTCCCCACCAC 1511
CCTTGCCAGGGCCCCAAGTTTGTAAATGGCTGAGGGAAAAGAGAGACAGAGGAGAGAGAGAGAAATGGAGGA 1583
GAAAGAGAGAGAGACAGAGAGGAGAGAGAGACAGTGAGAGAGACAGAAGAGAGAGAGAGACAAAGAGGAGAG 1655
AGAGAGAGTCAAAGAGAGAAAGAAAGAGAAAGAAATAGTAAAAAACAGTGTGCCCTATTCCTTTAAAAGCCA 1727
GGGTAAATTTAAAACCTGTACTTGATAATTGAAGGTCTTCTCTGTGACCCTATAGCACTCCAATCCACTTTG 1799
TGGTCAGTGTAAATAAGAGCATAGGCCGAAAGCACTGAGGCCATTGACAACCCGTAGCTTCCCTATCAAAAA 1871
TCCTTAACCCAGTAACCCGCAGATGGACCAAATGCATTCAGTCGGTAGCGCAACTGCTTTGCTAAAAGTAGA 1943
AAAGTAACTTTTAGAGGAAACCTCATTGTGAGCACACCTCACCTGTTCAGAATTATTCTAATAAAAAAAGCA 2015
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ACCAGACCTAGGCGGAACTCCCTTCAGGACAGGACGATAGATGGTTCCTCCCAGGTGATTGAGGAAAAAAAC 2231
CACAATGGGTATTCAGTAATTGATACGGGGACTCTTGTGGAAGCAGAGTTAGAAAAATTGCCTAATAACTGG 2303
TCTCCTCAAACGTGTGAGCTGTTTGCACTCAGCCAAGCCTTAAAGTACTTACAGAATCAAAAGACTATCTCA 2375
ATCCTGATTCAAAAGGTTAGCTACACCCTCTCTGTAATGCATTTGCATAAGAACTTGTTTATGGGAATGCAT 2447
CTTGATGGGGCAGCTGGGTTGTTATAAAATAGGAACCCAGCCCAGCTCTAGGACTCACCCCTGAGCGCAAAG 2519 tandem
GCAATGTTGGGCATGCTGGTAAAGGACCACTAGAATCCAGCAGCCCAGACCCCTTTCTTTGTGGTCAAGAAA 2591 repeat
GGCGGGAAAAGGGGTGCAGGACTGCTACATCGGTAAGCATAACTAATCCGATAAACAGAGGTCCATGGGTGG 2663 regions
TTACGCACCCTGGAAAGGAACTCACCCCTGAGCACAAAGGCAATGTTGGGCACGCTGGTAAAGGACCACTAG 2735 R2
AATCCAGCAGCCTGGACCCCTTTCTTTGTGGTCAAGAGAGGCAGGAAAACAGGTGCAGGACTGCAACATCAG 2807
TGAGCATAACTAATTCGATAAGCAGAGGTCCATGGGTGGTGATGCACCCTGGAAAGAATAAGCATTAGGACC 2879
ATAGAGGACACTCCAGGACTAAAGCTCATCGGAAAATGACTAGGGTTGCTGGCATCCCTATGTTCTTTTTC 2951
AGATGGGAAACGTTCCCCGCAAGACAAAAACGCCCCTAAGACGTATTCTGGAGAATTGGGACCAATTTGACC 3023
CTCAGACACTAAGAAAGAAACGACTTATATTCTTCTGCAGTGCCGCCTGGCACTCCTGAGGGAAGTATAAAT 3095
TATAACACCATCTTACAGCTAGACCTCTTTTGTAGAAAAGGCAAATGGAGTGAAGTGCCATAAGTACAAACC 3167
TTCTTTTCATTAAGAGACAACTCACAATTATGTAAAAAGTGTGATTTATGCCCTACAGGAAGCCTTCAGAGT 3239
CTACCTCCCTATCCCAGCATCCCCGACTCCTTCCCCAACTAATAAGGACCCCCCTTCAACCCAAATGGTCCA 3311
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AACAGACTTAGGTAAATTCTCAGATAACCCTGATGGCTATATTGATGTTTTACAAGGGTTAGGACAATTCTT 3527
TGATCTGACATGGAGAGATATAATGTCACTGCTAAATCAGACACTAACCCCAAATGAGAGAAGTGCCACCAT 3599 gag
AACTGCAGCCTGAGAGTTTGGCGATCTCTGGTATCTCAGTCAGGTCAATGATAGGATGACAACAGAGGAAAG 3671 domain
AGAATGATTCCCCACAGGCCAGCAGGCAGTTCCCAGTCTAGACCCTCATTGGGACACAGAATCAGAACATGG 3743
AGATTGGTGCTGCAGACATTTGCTAACTTGTGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGTCTATGAA 3815
TTACTCAATGATGTCCACCATAACACAGGGAAGGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGA 3887
GGCATTGAGGAAGCGTGCCTCTCTGTCACCTGACTCTTCTGAAGGCCAACTAATCTTAAAGCGTAAGTTTAT 3959
CACTCAGTCAGCTGCAGACATTAGAAAAAAACTTCAAAAGTCTGCCGTAGGCCCGGAGCAAAACTTAGAAAC 4031
CCTATTGAACTTGGCAACCTCGGTTTTTTATAATAGAGATCAGGAGGAGCAGGCGGAACAGGACAAACGGGA 4103
TTAAAAAAAAGGCCACCGCTTTAGTCATGACCCTCAGGCAAGTGGACTTTGGAGGCTCTGGAAAAGGGAAAA 4175
GCTGGGCAAATTGAATGCCTAATAGGGCTTGCTTCCAGTGCGGTCTACAAGGACACTTTAAAAAAGATTGTC 4247
CAAGTAGAAGTAAGCCGCCCCCTCGTCCATGCCCCTTATTTCAAGGGAATCACTGGAAGGCCCACTGCCCCA 4319
GGGGACAAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATGATCCAGCAGCAGGACTGAGGGTGCCTGGGGC 4391
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TCTTTTCACATGCTTTTCTAATTATGCTTGAAAGCCCCACTACCTTGTTAGGGAGAGACATTCTAGCAAAAG 4679
CAGGGGCCATTATACACCTGAACATAGGAGAAGGAACACCCGTTTGTTGTCCCCTGCTTGAGGAAGGAATTA 4751
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AGGATTCCACCTCCTTTCCCTACCAAAGGCAGTACCCCCTCAGACCCAAGGCCCAACAAGGACTCCAAAAGA 4895
TTGTTAAGGACCTAAAAGCCCAAGGCCTAGTAAAACCATGCAGTAACCCCTGCAGTACTCCAATTTTAGGAG 4967 pol
TACAGAAACCCAACAGACAGTGGAGGTTAGTGCAAGATCTCAGGATTATCAATGAGGCTGTTGTTCCTCTAT 5039 domain
AGCCAGCTGTACCTAGCCCTTATACTCTGCTTTCCCAAATACCAGAGGAAGCAGAGTGGTTTACAGTCCTGG 5111
ACCTTCAGGATGCCTTCTTCTGCATCCCTGTACATCCTGACTCTCAATTCTTGTTTGCCTTTGAAGATACTT 5183

FIGURE 1.1

CAAACCCAACATCTCAACTCACCTGGACTATTTTACCCCAAGGGTTCAGGGATAGTCCCCATCTATTTGGCC 5255
AGGCATTAGCCCAAGACTTGAGCCAATCCTCATACCTGGACACTTGTCCTTCGGTAGGTGGATGATTTACTT 5327
TTGGCCGCCCATTCAGAAACCTTGTGCCATCAAGCCACCCAAGCGCTCTTCAATTTCCTCGCTACCTGTGGC 5399
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ATACACTAATTAAGGAAACTCAGAAAGCCAATACCCATTTAGTAAGATGGACAACTGAAGTAGAAGTGGCTT 5687
TCCAGGCCCTAACCCAAGCCCCAGTGTTAAGTTTGCCAACAGGGCAAGACTTTTCTTCATATGTCACAGAAA 5759
AACAGGAATAGCTCTAGGAGTCCTTACACAGATCCGAGGGATGAGCTTGCAACCTGTGGCATACCTGACCA 5831
AGGAAATTGATGTAGTGGCAAAGGGTTGACCTCATTGTTTACGGGTAGTGGTGGCAGTAGCAGTCTTAGTAT 5903
CTGAAGCAGTTAAAATAATACAGGGAAGAGATCTTACTGTGTGGACATCTCATGATGTGAATGGCATACTCA 5975
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TGCTGCGACTGTGCACTTGTGCAACTCTTAACCCAGCCACATTTCTTCCAGACAATGAAGAAAAGATAAAAC 6119
ATAACTGTCAACAAGTAATTTCTCAAACCTATGCCACTCGAGGGGACCTTTTAGAGGTTCCTTTGACTGATC 6191
CCGACCTCAACTTGTATACTGATGGAAGTTCCTTTGTAGAAAAAGGACTTCGAAAAGTGGGGTATGCAGTGG 6263
TCAGTGATAATGGAATACTTGAAAGTAATCCCCTCACTCCAGGAACTAGTGCTCAGCTAGCAGAACTAATAG 6335
CCCTCACTTGGGCACTAGAATTAGGAGAAGAAAAAAGGGCAAATATATATACAGACTCTAAATATGCTTACC 6407
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TTCAGTATCTACTAGTCTGGGTAGATACTTTCACGGGTTGGGCAGAGGCCTTCCCCTGTAGGACAGAAAAGG 7127
CCCAAGAGGTAATAAAGGCACTAGTTCATGAAATAATTCCCAGATTCGGACTTCCCCGAGGCTTACAGAGTG 7199
ACAATAGCCCTGCTTTCCAGGCCACAGTAACCCAGGGAGTATCCCAGGCGTTAGGTATACGATATCACTTAC 7271
ACTGCGCCTGAAGGCCACAGTCCTCAGGGAAGGTCGAGAAAATGAATGAAACACTCAAAGGACATCTAAAAA 7343
AGCAAACCCAGGAAACCCACCTCACATGGCCTGCTCTGTTGCCTATAGCCTTAAAAAGAATCTGCAACTTTC 7415
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AGGAACCTATCCCTGAGAAGAGGGAAAAGAACTATTCCACCCTTGTGACATGGTATTAGTCAAGTCCCTTCC 7631
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ACCCTCTTTCACTCTCACTGCACCCCCTCCATGCCGCTGTATGACCAGTAGCTCCCCTTACCAAGAGTTTCT 7991
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TTGGACAGGAAAAATGATTAATCCTAGTTGTCCTGGAGGACTTGGAGTCACTGTCTGTTGGACTTACTTCAC 8207 env
CCAAACTGGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAAGAGAAAAACATGTAAAAGAAGTAATCTC 8279
CCAACTCACCCGGGTACATGGCACCTCTAGCCCCTACAAAGGACTAGATCTCTCAAAACTACATGAAACCCT 8351 domain
CCGTACCCATACTCGCCTGGTAAGCCTATTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGCCCAAAA 8423
CCCTACTAACTGTTGGATATGCCTCCCCCTGAACTTCAGGCCATATGTTTCAATCCCTGTACCTGAACAATG 8495
GAACAACTTCAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCTCTTGTTTCCAATCTGGAAATAAC 8567
CCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTACATACACAACCAACTCCCAATGCATCAGGTG 8639
GGTAACTCCTCCCACACAAATAGTCTGCCTACCCTCAGGAATATTTTTTGTCTGTGGTACCTCAGCCTATCG 8711
TTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCATTCTTAGTGCCCCCTATGACCATCTACACTGA 8783
ACAAGATTTATACAGTTATGTCATATCTAAGCCCCGCAACAAAAGAGTACCCATTCTTCCTTTTGTTATAGG 8855
AGCAGGAGTGCTAGGTGCACTAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAAACT 8927
ATCTCAAGAACTAAATGGGGACATGGAACGGGTCGCCGACTCCCTGGTCACCTTGCAAGATCAACTTAACTC 8999
CCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGGGAACCTGTTT 9071
ATTTTTAGGGGAAGAATGCTGTTATTATGTTAATCAATCCGGAATCGTCACTGAGAAAGTTAAAGAAATTCG 9143
AGATCGAATACAACGTAGAGCAGAGGAGCTTCGAAACACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCC 9215
CTGGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTCTTTGGACCCTGTATCTTTAA 9287
CCTCCTTGTTAACTTTGTCTCTTCCAGAATCGAAGCTGTAAAACTACAAATGGAGCCCAAGATGCAGTCCAA 9359
GACTAAGATCTACCGCAGACCCCTGGACCGGCCTGCTAGCCCACGATCTGATGTTAATGACATCAAAGGCAC 9431
CCCTCCTGAGGAAATCTCAGCTGCACAACCTCTACTAGGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTC 9503
TCGGCCAACCTCCCCAACAGCACTTAGGTTTTCCTGTTGAGATGGGGGACTGAGAGACAGGACTAGCTGGAT 9575
TTCCTAGGCTGACTAAGAATCCCTAAGCCTAGCTGGGAAGGTGACCACATCCACCTTTAAACACGGGGCTTG 9647
CAACTTAGCTCACACCTGACCAATCAGAGAGCTCACTAAAATGCTAATTAGGCAAAGACAGGAGGTAAAGAA 9719
ATAGCCAATCATCTATTGCCTGAGAGCACAGCAGGAGGGACAATGATCGGGATATAAACCCAAGTCTTCGAG 9791 repeat
CCGGCAACGGCAACCCCCTTTGGGTCCCCTCCCTTTGTATGGGAGCTCTGTTTTCATGCTATTTCACTCTAT 9863 region
TAAATCTTGCAACTGCACTCTTCTGGTCCATGTTTCTTACGGCTTGAGCTGAGCTTTCGCTCGCCATCCACC 9935
ACTGCTGTTTGCCGCCACCGCAGACCCGCCGCTGACTCCCATCCCTCTGGATCATGCAGGGTGTCCGCTGTG 10007 R1
CTCCTGATCCAGCGAGGCACCCATTGCCGCTCCCAATCGGGCTAAAGGCTTGCCATTGTTCCTGCATGGCTA 10079
AGTGCCTGGGTTCATCCTAATTGAGCTGAACACTAGTCACTGGGTTCCATGGTTCTCTTCTGTGACCCACAG 10151
CTTCTAATAGAGCTATAACACTCACCGCATGGCCCAAGGTTCCATTCCTTGAATCCATAAGGCCAAGAACCC 10223
CAGGTCAGAGAACACGAGGCTTGCCACCATCTTGGGAGCTCTGTGAGCAAGGACCCCCAAGTAACACAACCA 10295
TGAGGGTGCAAATGCATGGGCCACTAATGGTAGAGCAAGAAAACAGAAGGGCCCTGGTTCCTCGAAGGCATC 10367
AGTGAGCTGAAATGCCTGCCCTGGATGTCCTATTCCTAGGTGTTTTTCTGCCTGAAGCAGATTAAACCCTTT 10439
GTTCACTTCTCCAAGTAGGGCTTCTATTACAGCCCAAATCAATCCCCACCCCAGATGACAT 10500

FIGURE 1.2

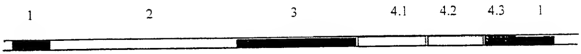

FIGURE 2

```
ACTGAGAGACAGGACTAGCTGGATTTCCTAGGCCGACTAAGAATCCCTAAGCCTAGCTGGGAAGGTGACC
::::::::::::::::::::::::::::::::: ::::::::::::::::::::::::::::::::::::
ACTGAGAGACAGGACTAGCTGGATTTCCTAGGCTGACTAAGAATCCCTAAGCCTAGCTGGGAAGGTGACC
ACGTCCACCTTTAAACACGGGGCTTGCAACTTAGCTCACACCTGACCAATCAGAGAGCTCACTAAAATGC
:: :::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
ACATCCACCTTTAAACACGGGGCTTGCAACTTAGCTCACACCTGACCAATCAGAGAGCTCACTAAAATGC
TAATTAGGCAAAGACAGGAGGTAAAGAAATAGCCAATCATCTATTGCCTGAGAGCACAGCAGGAGGGACA
::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
TAATTAGGCAAAGACAGGAGGTAAAGAAATAGCCAATCATCTATTGCCTGAGAGCACAGCAGGAGGGACA
ACAATCGGGATATAAACCCAGGCATTCGAGCTGGCAACAGCAGCCCCCCTTTGGGTCCCTTCCCTTTGTA
:  ::::::::::::::::: :  ::::::: :::::: ::: ::::: :::::::::: ::::::::::
ATGATCGGGATATAAACCCAAGTCTTCGAGCCGGCAACGGCAACCCCC-TTTGGGTCCCCTCCCTTTGTA
TGGGAGCT--GTTTTCATGCTATTTCACTCTATTAAATCTTGCAACTGCACTCTTCTGGTCCATGTTTCT
::::::::  ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
TGGGAGCTCTGTTTTCATGCTATTTCACTCTATTAAATCTTGCAACTGCACTCTTCTGGTCCATGTTTCT
TACGGCTCGAGCTGAGCTTTTGCTCACCGTCCACCACTGCTGTTTGCCACCACCGCAGACCTGCCGCTGA
::::::: :::::::::::: :::: :: ::::::::::::::::::: :::::::::::: ::::::::
TACGGCTTGAGCTGAGCTTTCGCTCGCCATCCACCACTGCTGTTTGCCGCCACCGCAGACCCGCCGCTGA
CTCCCATCCCTCTGGATCCTGCAGGGTGTCCGCTGTGCTCCTGATCCAGCGAGGCGCCCATTGCCGCTCC
:::::::::::::::::: :::::::::::::::::::::::::::::::::::: ::::::::::::::
CTCCCATCCCTCTGGATCATGCAGGGTGTCCGCTGTGCTCCTGATCCAGCGAGGCACCCATTGCCGCTCC
CAATTGGGCTAAAGGCTTGCCATTGTTCCTGCACGGCTAAGTGCCTGGGTTTGTTCTAATTGAGCTGAAC
:::: :::::::::::::::::::::::::::: :::::::::::::::::  : :::::::::::::::
CAATCGGGCTAAAGGCTTGCCATTGTTCCTGCATGGCTAAGTGCCTGGGTTCATCCTAATTGAGCTGAAC
ACTAGTCACTGGGTTCCATGGTTCTCTTCTGTGACCCACGGCTTCTAATAGAACTATAACACTTACCACA
::::::::::::::::::::::::::::::::::::::: :::::::::::: :::::::::: ::: ::
ACTAGTCACTGGGTTCCATGGTTCTCTTCTGTGACCCACAGCTTCTAATAGAGCTATAACACTCACCGCA
TGGCCCAAGATTCCATTCCTTGGAATCCGTGAGGCCAAGAACTCCAGGTCAGAGAATACGAGGCTTGCCA
::::::::: :::::::::::: ::::: : ::::::::::: ::::::::::::: :::::::::::::
TGGCCCAAGGTTCCATTCCTTG-AATCCATAAGGCCAAGAACCCCAGGTCAGAGAACACGAGGCTTGCCA
CCATCTTGGAAGC
::::::::: :::
CCATCTTGGGAGC
```

FIGURE 3

IPMALPYHIFLFTVLLPSFTLTAPPPCRCMTSSSPYQEFLWRMQRPGNIDAPSYRSLSKG
TPTFTAHTHMPRNCYHSATLCMHANTHYWTGKMINPSCPGGLGVTVCWTYFTQTGMSDGG
GVQDQAREKHVKEVISQLTRVHGTSSPYKGLDLSKLHETLRTHTRLVSLFNTTLTGLHEV
SAQNPTNCWICLPLNFRPYVSIPVPEQWNNFSTEINTTSVLVGPLVSNLEITHTSNLTCV
KFSNTTYTTNSQCIRWVTPPTQIVCLPSGIFFVCGTSAYRCLNGSSESMCFLSFLVPPMT
IYTEQDLYSYVISKPRNKRVPILPFVIGAGVLGALGTGIGGITTSTQFYYKLSQELNGDM
ERVA**DSLVTLQDQLNSLAAVVLQNRRALDLLTAERGGTCLFLGEECCYYVNQSGIVTEKVKEIRDRIQRRAEELR**
NTGPWGLLSQWMPWILPFLGPLAAIILLLLFGPCIFNLLVNFVSSRIEAVKLQMEPKMQSKTKIYRRPLDRPASP
RSDVNDIKGTPPEEISAAQPLLRPNSAGSS

FIGURE 4

1)	NSLAAVVLQNRRALDLLTAESGGTFLFLEEKC
2)	NSLAAVVLQNRRALDLLTAERGGTCLFLGEEC
3)	DSLAAVTLQNHQGLDLLTAEKGGLCYFLGEDC
4)	DSLAAVTLQNHQGLDLLIAEKGGLCTFLGEEC
5)	DSLAAVTLQNCRGLDLLTAEKGGHYTFLGEEC
6)	LQNRRGLDLLFLKEGGLC
7)	DSLAKVVLQNRRGLDLLTAEQGGICLALQEKC

FIGURE 5

TSFVEKANGVKCHKYKLSFHXETTHNYVKSVIYALQEAFRVYLPILPASPTPSPTNKDPPSTQMVQKEIDKRVNSEPKS
ANIPQLXPLQAVGGREFGPARVHVPFSLPDLKQIKTDLGKFSDNPDGYIDVLQGLGQFFDLTWRDIMSLLNQTLTPNER
SATITAAXEFGDLWYLSQVNDRMTTEEREXFPTGQQAVPSLDPHWDTESEHGDWCCRHLLTCVLEGLRKTRKKSMNYSM
MSTITQGREENPTAFLERLREALRKRASLSPDSSEGQLILKRKFITQSAADIRKKLQKSAVGPEQNLETLLNLATSVFY
NRDQEEQAEQDKRDXKKGHRFSHDPQASGLWRLWKREKLGKLNAXXGLLPVRSTRTLXKRLSKXKXAAPSSMPLISRES
LEGPLPQGTKVLXVRSHXPD/SSSRT

FIGURE 6

```
CCTGGCACTCCTGAGGGAAGTATAAATTATAACACCATCTTACAGCTAGACCTCTTTTGTAGAAAAGGCA
:::::: :::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
CCTGGC-CTCCTGAGGGAAGTATAAATTATAACACCATCTTACAGCTAGACCTCTTTTGTAGAAAAGAAG
-CAAATGGAGTGAAGTGCCATAAGTACAAACTTTCTTTTCATTAAGAGACAACTCACAATTATGTAAAAA
 ::::::::::::::::::::: ::::::::::::::::::::::::: ::::: ::::::::::::::
GCAAATGGAGTGAAGTGCCATATGTACAAACTTTCTTTTCATTAAGAGATAACTCCCAATTATGTAAAAA
GTGTGATTTATGCCCTACAGGAAGCCTTCAGAGTCTACCTCCCTATCCCAGCAT--CCCCGACTCCTTCC
:::::::::::::::::::::::: :::::::::::::::: : :::::::   :::: ::::::::
GTGTGATTTATGCCCTACAGGAAGCCCTCAGAGTCTACCTCCCGACCCCAGCAAGACCCCAACTCCTTCT
CCAACTAATAAGGACCCCCCTTCAACCCAAATGGTCCAAAAGGAGATAGACAAAAGGGTAAACAGTGAAC
::::::::::::::::::::::::::::::::::::::::::::::::::::: ::::::::: :::::
CCAACTAATAAGGACCCCCCTTCAACCCAAATGGTCCAAAAGGAGATAGACAAAGGGGTAAACAATGAAC
CAAAGAGTGCCAATATTCCCCAATTATGACCC-CTCCAAGCAGTGGGAGGAAGAGAATTCGGCCCAGCCA
:::::::::::::::: : : ::::: :: : ::::::::::::::::::: :: : :: ::::::::::
CAAAGAGTGCCAATATTACACGATTAT-ACTCGCTCCAAGCAGTGGGAGGA-GA-ATTT-GGCCCAGCCA
GAGTGCATGTGCCTTTTTCTCTCCCAGACTTAAAGCAAATAAAAACAGACTTAGGTAAATTCTCAGATAA
: :::::::: ::::::::::: :::: ::::::::::: :::: :::: ::::::::::::::::::::
GCGTGCATGTACCTTTTTCTCTCTCAGATTTAAAGCAAATTAAAATAGACCTAGGTAAATTCTCAGATAA
CCCTGATGGCTATATTGATGTTTTACAAGGGTTAGGACAATTCTTTGATCTGACATGGAGAGATATAATG
:::::::::::::::::::::::::::::::::::::::::: :::::::::::::::::::::::::::
CCCTGATGGCTATATTGATGTTTTACAAGGGTTAGGACAATCCTTTGATCTGACATGGAGAGATATAATG
TCACTGCTAAATCAGACACTAACCCCAAATGAGAGAAGTGCCACCATAACTGCAGCCTGAGAGTTTGGCG
: :::::::::::::::::::::::::::: : ::::::  ::::::: :::::::::::::::::::
TTACTGCTAAATCAGACACTAACCCCAAATGAAAAAAGTGCTGCCATAACAGCAGCCTGAGAGTTTGGCG
ATCTCTGGTATCTCAGTCAGGTCAATGATAGGATGACAACAGAGGAAAGAGAATGATTCCCCACAGGCCA
: :::::::::::::::::::::::::::::::::::::::: ::::::::::::::::::::::::::
AACTCTGGTATCTCAGTCAGGTCAATGATAGGATGACAACAGATGAAAGAGAATGATTCCCCACAGGCCA
GCAGGCAGTTCCCAGTCTAGACCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCTGCAGACAT
:::::::::::::::: ::::::::::: ::::::::::::::::: ::::::::::::  :::::::
GCAGGCAGTTCCCAGTGTAGACCCTCATTAGGACACAGAATCAGAACTTGGAGATTGGTGCCACAGACAT
TTGCTAACTTGTGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGTCTATGAATTACTCAATGATGTCCA
:::::::::: :::::::::::::::::::::::::::::: : ::::::: :::::::::::
TTGCTAACTTGCGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGCCCATGAATTATTCAATGATGTCCC
CCATAACACAGGGAAGGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAGGAAGCG
: ::::::::::::: :::::::::::::::::::::::::::::::::::::: : ::::::::::
CTATAACACAGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAAGGATTGAGGAAGCA
TGCCTCTCTGTCACCTGACTCTTCTGAAGGCCAACTAATCTTAAAGCGTAAGTTTATCACTCAGTCAGCT
: :::: :::::::::::::::::  : ::::::::::::::::::::::  ::::::::::::::::::::
TACCTCCCTGTCACCTGACTCTATTAAAGGCCAACTAATCTTAAAGGATAAGTTTATCACTCAGTCAGCT
GCAGACATTAGAAAAAAACTTCAAAAGTCTGCCGTAGGCCCGGAGCAAAACTTAGAAACCCTATTGAACT
::::: ::::  :::::::::::::::: :::: ::::::: :::::::::::::::::::: ::::::
GCAGAGATTAAGAAAAAACTTCAAAAGTATGCCTTAGGCCCAGAGCAAAACTTAGAAACCCTACTGAACT
TGGCAACCTCGGTTTTTATAATAGAGATCAGGAGGAGCAGGCGGAACAGGACAAACGGGATTAAAAAAA
:::::::::: ::::::::::::::::::::::: ::::::: ::::  ::::::: ::::: :::::::
TGGCAACCTCAGTTTTTATAATAGAGATCAGGAAGAGCAGG-GGAATGGGACAAATGGGATAAAAAAAA
A-------GGCCACCGCTTTAGTCATGACCCTCAGGCAAGTGGACTTTGGAGGCTCTGGAAAAGGGAAAA
:       ::  :: ::::::::: :: ::::::::::: ::::::::::::::::  ::::::::::::
AAAAAAAAGGTGACTGCTTTAGTCGTGGCCCTCAGGCAAATGGACTTTGGAGGCTCCAGAAAAGGGAAAA
GCTGGGCAAATTGAATGCCTAATAGGGCTTGCTTCCAGTGCGGTCTACAAGGACACTTTAAAAAAGATTG
:::: ::::::::::::::::: ::::::::::::: :::: ::::::::::::::::::::::::::::
GCTGAGCAAATTGAATGCCTAACAGGGCTTGCTTCTAGTGTGGTCTACAAGGACACTTTAAAAAAGATTG
TCCAAGTAGAAGTAAGCCGCCCCCTCGTCCATGCCCCTTATTTCAAGGGAATCACTGGAAGGCCCACTGC
:::::::::::  :::: ::::::: :::::::::::::::: ::::::::::::::::::::::::::
TCCAAGTAGAAACAAGCTGCCCCCTTGTCCATGCCCCTTATGTCAAGGGAATCACTGGAAGGCCCACTGC
CCCAGGGGACAAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATGATCCAGCAGCAGGACTGAGGGTGCC
:::::: ::  ::::::::::::::::::::::::::::::::: ::::::::::::::::::: ::::
CCCAGGAGATGAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATAATCCAGCAGCAGGACTGAGGATGCC
TGGGGCAAGCGCCATCCCATGCCATCACCCTCACAGAGCCCTGGGTATGCTTGACCATTGAGGGCCAGGA
  ::::::::::::: :::::::::::::::::::::::: ::::::::::::::::::::::::::::
CAGGGCAAGCGCCAGCCCATGCCATCACCCTCACAGAGCCTTGGGTATGCTTGACCATTGAGGGCCAGGA
GGTT----GTCTCCTGGACACTGGTGCGGTCTTCTTAGTCTTACTCTTCTGTCCCGGACAACTGTCCTCC
::::    ::::: :::::::::::  :: ::::: ::::::::::: :::::: ::::::::::::: :
GGTTCACTGTCTCTTGGACACTGGTATGGCCTTCTCAGTCTTACTCTCCTGTCCTGGACAACTGTCCTTC
```

FIGURE 7

```
01/                              TAAATCCCCATGGCCCTCCCTTATCATATTTTTCT
02/                              TAAATCCCC-TGGCCCTCCCTTATCATATTTTTCT
03/                              TAAATCCCCATGGCCCTCCCTTATCATATTTTTCT
04/                              TAGATCCTCATGGCCCTCC-TTGTCATATTTTTTT

01/CTTTACTGTTCTTTTA-CCCTCTTTCACTCTCACTGCACCCCCTCCATGCCGCTGTATGACC
02/CTTTACTGTTCTCTTACCCCCCTTTCACTCTCACTGCACCCCGTCCATGCCACTGCACCCCC
03/CTTTACTGTTCTCTTA-CCCCCTTTCTCTCTCACTGCACCCCCTCCATGCTGCTGTACAACC
04/CTTTACTGTTCTCTTA-CCCCCTTTCACTCTCACTGAACCCCCTCCATGCCACTGTACTACC

01/AGT--------------------AGCTCCCCTTACCAAGAGTTTCTATGGAGAATGCAGCGT
02/GTCCATGCCCGTCTCATGCCAGTAGCTCCCCTTAGCAAGAGTTTCTATGGAGAATGCAGCGT
03/AGC--------------------AGCTCCCCTTACCAAGAGTTTCTATGAAGAATGCGGCTT
04/AGT--------------------AGCTCCCATTACCAAGAGCTTCTATGGACAATGCGGCTT

01/CCCGGAAATATTGATGCCCCATCGTATAGGAGTCTTTCTAAGGGAACCCCCACCTTCACTGC
02/CCCGGAAATATTGATGCCCCATTGTATAGGAGTTTATCTAAGGGAACCCCCACCTTCACTGC
03/CCCAGAAATATTGATGCCCCATCAAATAGGAGTTTACCTAAAGGAAACTCCACCTTCACTGC
04/CCTGGAAATATTGATGACCCATCGTATAGGAGTTTTTCTAAAGGAAACCCCATTTTCACCAC

01/CCACACCCATATGCCCCGCAACTGCTATCACTCTGCCACTCTTTGCATGCATGCAAATACTC
02/CCACACCCATATGCCCCACAACTGCTATAACTCTGCCACTCTTTGCATGCATGCAAATACTC
03/CCACACCCATATGCCCCACAACTGCTATAACTCTGCCACTCTTTGCATGCATGCAAATACTC
04/CCACACCTATATGACCC---------------------------------------------

01/ATTATTGGACAGGAAAAATGATTAATCCTAGTTGTCCTGGAGGACTTGGAGTCACTGTCTGT
02/ATTATTGGACAGGAAAAACGATTAATCCCAGTTGTCCTGGAGGACTTGGAG-----------
03/ATTATTGGACAGGGAAAATGATTAATCCTAGTTGTCCTGGAAGACTTGGAGCCACTGTCTGT
04/--------------------------------------------------------------

01/TGGACTTACTTCACCCAAACTGGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAAGAGA
02/--GACTCACTTCACTCATACCAGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAACAGA
03/CGGACTTACTTCACCCATACTGGTATGTCTGAGGGGGGTGGAGTTCAAGATCAGGCAAGAGA
04/--------------------------------------------------------------

01/AAAACATGTAAAAGAAGTAATCTCCCAACTCACCCGGGTACATGGCACCTCTAGCCCCTACA
02/AAAACACATAAAGGAAGTAATCTCCCAACTGACCTGGGTACATAGCACCCCTGGCCCCTACA
03/AAAACATGTAAAGGAAGTAACCTCCCAACTGACCCGGGTACATAGCACCCCTAGCCCCTACA
04/--------------------------------------------------------------

01/AAGGACTAGATCTCTCAAAACTACATGAAACCCTCCGTACCCATACTCGCCTGGTAAGCCTA
02/AAGGACTAGATCTCTCAAAACTACATGAAACCCTCCATACCCATACTGGCCTGGTAAGCCTA
03/AAGGACTAGATCTCTTAAAACTACATGAAACCCTCCATACCCATACTTGCCTGGTAAGCCTA
04/--------------------------------------------------------------

01/TTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGCCCAAAACCCTACTAACTGTTGGAT
02/TTTAATACCACCCTGACTGGGCTCCATGAGGTCTCGGCCCAAAACCCTACTAACTGTTGGAT
03/TTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGTCCAAAACCCTACTAACTGTTGGTT
04/--------------------------------------------------------------

01/ATGCCTCCCCCTGAACTTCAGGCCATATGTTTCAATCCCTGTACCTGAACAATGGAACAACT
02/GTGCCTCCCCCTGCACTTTAGGCCATACATTTCAATCCCTATACCTGAACAATGGAACAACT
03/GTGCCTCCCCCTGTATTTCAGGCCATGCATTTCAATCCCTGTACCTGAACAATGGAACAACT
04/-----------TGCACTTCAGGCCATACATTTCAATCCCTGTA-------------------
```

FIGURE 8.1

01/TCAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCTCTTGTTTCCAATCTGGAAATA
02/TCAGCACAGAAATAAACACCACTTCTGTTTTAGTAGGTCCTC---TTTCCAATCTGGAAATA
03/ACAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCTCTTGTTTCCAATCTGGAAATA

01/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTACATACACAACCAACTCCCA
02/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTATAGACACAGCCAACTCCCA
03/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTGTAGACACAACCAACTCCCA
04/---

01/ATGCATCAGGTGGGTAACTCCTCCCACACAAATAGTCTGCCTACCCTCAGGAATATTTTTTG
02/ATGCATCAGGTGGGTAACTCCTCCCACACGAATAGTCTGCCTACCCTCAGGAATATTTTTTG
03/ATGCATCAGGTGGGTAACTCCTCCCACACGAATAGTCTGCCTACCCTCAGGAATATTTTTTG
04/---

01/TCTGTGGTACCTCAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCA
02/TCTGTGGTACCTCAGCCTATCATTGTTTGAATGGCTCTTCAGAATCTGTGTGCTTCCTCTCA
03/TCTGTGGTACCTTAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCA
04/---

01/TTCTTAGTGCCCCCTATGACCATCTACACTGAACAAGATTTATACAGTTATGTCATATCTAA
02/TTCTTAGTGGCCCCTATGCCCATCTACACTGAACAAGATTTATACAATCATGTCATACCTAA
03/TTCTTAGTGCCCCC-ATGACCATTTACACTGAACAAGATTTATACAATTATGTTGTACCTAA
04/---

01/GCCCCGCAACAAAAGAGTACCCATTCTTCCTTTTGTTATAGGAGCAGGAGTGCTAGGTGCAC
02/GCCCCGCAACAAAAGAGTACCCATTCTTCCTTTTGTTATTGGAGCAGGAGTGCTAGGCGGAG
03/GCCCCACAACAAAAGAGTACTCATTCTTCCTTTTGTTATCGGAGCAGGAGTGCTAGGTGGAC
04/---

01/TAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAAACTATCTCAAGAA
02/TAGCTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAAACTGTCTCAAGAA
03/TAGGTTCTGGCATTGGCGGTACCACAACCTCTACTCAGTTCTACTACAAACTATCTCAAGAA
04/---

01/CTAAATGGGGACATGGAACGGGTCGCCGACTCCCTGGTCACCTTGCAAGATCAACTTAACTC
02/CTTAAAGGTGACATGGAATGGGTCGCTGATACCCTGGTCACCTTGCAAGATCAACTTAACTC
03/CTCAATGGTGACATGGAATGGGTTGCCGACTCCCTGGTCACCTTGCAAGATCAACTTAACTT
04/---

01/CCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGG
02/CCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCGGAAAGCGGGG
03/CCTAGCATCAGTAGTCCTTCAAAATTGAAGAGCTTTAGACTTGCTAACCTCTGAAAGAGGGG
04/---

01/GAACCTGTTTATTTTTAGGGGAAGAATGCTGTTATTATGTT---------------------
02/GAACCTTTTTATTTTTAGAGGAAAAATGCTGTTGTTATGTT---------------------
03/GAAGCTGTTTATTTTTAGGGGAAGAATGTTGTTATTATGTTATTTTAGCGGAAGAATGTTGT
04/---

01/---------AATCAATCCGGAATCGTCACTGAGAAAGTTAAAGAAATTCGAGATCGAATACA
02/---------AATCAATCCGGAATCATCACCGAGAAAGTTAAAGAAATTCAAGGTCGAATATA
03/TATTATGTTAATCAATCCTGAATTGTCACAGAGAAAGTTGAAGAAATTCGAGATTGAATACA
04/---

01/ACGTAGAGCAGAGGAGCTTCGAAA-CACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
02/ACGTAGAGCAAAGGAGCTGCAAAA-CACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
03/ACGTAGAACAGAGGAGCTTCAAAAACACCAGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
04/--

FIGURE 8.2

01/GGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTCTTTGGACCCTGTA
02/GGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGTTACTCCTCTTTGGACCCTGTA
03/GGATTCTCCCCTTCTTAGGATCTCTAGCAGCTCTAATATTGATACTCCTCTTTGGACCCTGTA
04/---

01/TCTTTAACCTCCTTGTTAACTTTGTCTCTTCCAGAATCGAAGCTGTAAAACTA----------
02/TCTTTAACCTCCTTGTTAAGTTTGTCTTTTCCAGAATCGAAGCAGTAAAACTACAAATCGTTC
03/TCTTTAACCTCCTTGTTAAGTTTGTCTCTTCCAGAATCAAAGTTGTAAAGCTACAAATCGTTC
04/TCTTTAACCTCCTTGTTAAGCTTGTCTCTTGCAGAATCGAAGCTGTAAAACTACAAATGCTTG

01/--CAAATGGAGCCCAAGATGCAGTCCAAGACTAAGATCTACCGCAGACCCCTGGACCGGCCTG
02/TTCAAATGGAGCCCCAGATGCAGTCCATGAGTAAAATCTACCACGGACCCCTGGACCGGCCTG
03/TTCAAATGGAACCCCAGATGAAGTCCATGACTAAGATCTACCGTGGACCCCTGGACCGGCCTA
04/TTAAAATAGAGCCCCAGATGCAGTCCATGGCTAAGATCTACCACGGACCCCTGGACCGGCCTG

01/CTAGCCCACGATCTGATGTTAATGACATCAAAGGCACCCCTCCTGAGGAAATCTCAGCTGCAC
02/CTAGCCCATGCTCTGATGTTAATGACATCAAAGGCACCCCTCCCGAGGAAATCTCAACTGCAC
03/CTAGCCCATGCTCCAATTGTAATGATATCGAACGCACCCCTCCCGAGGAAATCTCAACTGCAC
04/CTAGCCCATGCTCTGATGTTGATGACATTGAAGGCACGGCTTCCGAGGAAATCTCAACTGCAC

01/AACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCCCC
02/AACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGTGGTTGTTGGCCAACCTCCCC
03/AACCCCTACTATGCCCCAATTCCGCAGGAAGCAGTTAGACTGGTCGTCAGCCAACCTCCCC

04/GACCCCTACTACACCCCAATTTAGCGGGAAGCAATTAGAGCAGCCTATGGCCACCTCCCC

FIGURE 8.3

```
CTTCCCCAACTAATAAGGACCCCCCTTTCAACCCAAACAGTCCAAAAGGACATAGACAAAGGA    3
CTTCCCCAACTAATAAGGACCCCCCTTTCAACCCAAACAGTCCAAAAGGACATAGACAAAGGA    4
CTTCCCCAACTAATAAGGACCCCCC-TTCAACCCAAATGGTCCAAAAGGAGATAGACAAAAGG    5
CTTCTCCAACTAATAAGGACCCCCC-TTCAACCCAAATGGTCCAAAAGGAGATAGACAAAGGG    6
CTTCCCCAAATAATAAGAACCCCCC-TTCAACCCAAACGGTCCAAAAGGAGATAGACAAAGGG    7

GTAAACAATGAACCAAAGAGTGCCAATATTCCCTGGTTATGCACCCTCCAAGCGGTGGGAG--    3
GTAAACAATGAACCAAAGAGTGCCAATATTCCCTGGTTATGCACCCTCCAAGCGGTGGGAG--    4
GTAAACAGTGAACCAAAGAGTGCCAATATTCCCCAATTATGACCCCTCCAAGCAGTGGGAGGA    5
GTAAACAATGAACCAAAGAGTGCCAATATTACACGATTATACTCGCTCCAAGCAGTGGGAG--    6
GTAAACAACTAACCAAAGAATGCCAATATTCCCCGATTATGCCCCCTCCAAGCGGTGGGAG--    7

A-AGAATTCGGCCCAGCCAGAGTGCATGTACCTTTTTCTCTCTCAC-ACTTGAAGCAAATTAAA    3
A-AGAATTCGGCCCAGCCAGAGTGCATGTACCTTTTTCTCTCTCAC-ACTTGAAGCAAATTAAA    4
AGAGAATTCGGCCCAGCCAGAGTGCATGTGCCTTTTTCTCTCCCAG-ACTTAAAGCAAATAAAA    5
-GAGAATTTGGCCCAGCCAGCGTGCATGTACCTTTTTCTCTCTCAG-ATTTAAAGCAAATTAAA    6
-GAGAATTCGGCCCAGCCAGAGTGCACGTACCTTTTTCTCTCTCTAGACTTTAAA----TTAAA    7

ATAGACNTAGGTNAATTNTCAGATAGCCCTGATGGYTATATTGATGTTTTACAAGGATTAGGA    3
ATAGACXTAGGTXAATTXTCAGATAGCCCTGATGGXTATATTGATGTTTTACAAGGATTAGGA    4
ACAGACTTAGGTAAATTCTCAGATAACCCTGATGGCTATATTGATGTTTTACAAGGGTTAGGA    5
ATAGACCTAGGTAAATTCTCAGATAACCCTGATGGCTATATTGATGTTTTACAAGGGTTAGGA    6
ATAGACCTAGGTAAATTCTCAGATAACCCTAATGGCTATATTGATGTTTTACAAGGTTTAGGA    7

                                   TTCCTGAGTTCTTGCACTAACCTCAAAT    1
CAATCCTTTGATCTGACATGGAGAGATATAATATTACTGCTAAATCAGACGCTAACCTCAAAT    3
CAATCCTTTGATCTGACATGGAGAGATATAATATTACTGCTAAATCAGACGCTAACCTCAAAT    4
CAATTCTTTGATCTGACATGGAGAGATATAATGTCACTGCTAAATCAGACACTAACCCCAAAT    5
CAATCCTTTGATCTGACATGGAGAGATATAATGTTACTGCTAAATCAGACACTAACCCCAAAT    6
CAATCCTTTGATCTGATATGGAGAGATATAATGTTACTGCTAAATCAGACACTAACCCCAAAT    7

GAGAGAAGTGCCGCCATAACTGCAACCCAAGAGTTTGGCGATCCCTGGTATCTCAGTCAGGTC    1
GAGAGAAGTGCTGCCATAACTGGAGCCCGAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC    3
GAGAGAAGTGCTGCCATAACTGGAGCCCGAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC    4
GAGAGAAGTGCCACCATAACTGCAGCCTGAGAGTTTGGCGATCTCTGGTATCTCAGTCAGGTC    5
GAAAAAAGTGCTGCCATAACAGCAGCCTGAGAGTTTGGCGAACTCTGGTATCTCAGTCAGGTC    6
GACAGAAGTGTCGCCGTAACTGGAGCCCGAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC    7

AATGACAGGATGACAACAGAGGAAAGATAATGATTCCCCACAGGCCAGCAGGCAGTTCCCAGT    1
AATGATAGGATGACAACGGAGGAAAGAGAACGATTCCCCACAGGGCAGCAGGCAGTTCCCAGT    3
AATGATAGGATGACAACGGAGGAAAGAGAACGATTCCCCACAGGGCAGCAGGCAGTTCCCAGT    4
AATGATAGGATGACAACAGAGGAAAGAGAATGATTCCCCACAGGCCAGCAGGCAGTTCCCAGT    5
AATGATAGGATGACAACAGATGAAAGAGAATGATTCCCCACAGGCCAGCAGGCAGTTCCCAGT    6
AATGATAGGATGACAACAGAGGAAAGAGAACGATTCCCCACAGGCCAGCAGGCAGTTCCCAGT    7

GTAGACCCTCATTAGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTGCTAACT    1
                                                           AACT    2
GTAGCTCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTACTAACT    3
GTAGCTCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTT           4
CTAGACCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCTGCAGACATTTGCTAACT    5
GTAGACCCTCATTAGGACACAGAATCAGAACTTGGAGATTGGTGCCACAGACATTTGCTAACT    6
GTAGACCCTCACTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTGCTAACT    7
```

FIGURE 9.1

```
TGCGTGCTAGAAGGACTAAGGAAAACTAGGAAGA----TATGAATTATTCAATGATGTCCACT     1
TGCGTGCTAGAAGGACTAAGGAAAACTAGGAAGA---CTATGAATTATTCAATGATGTCCACT     2
TGCGTGCTAGAAGGACTAAGGAAAACTAGGAAGA---CTATGAATTATTCAATGATGTCCACT     3
TGTGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGTCTATGAATTACTCAATGATGTCCACA     5
TGCGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGCCCATGAATTATTCAATGATGTCCCCT     6
TGCGTGCTAGAAGGACTAAGGAAAACTAGAAAGAAGCCTGTGAGTTATTCAATGATGTCCACT     7

ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG     1
ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG     2
ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG     3
ATAACACAGGG-AAGGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG     5
ATAACACAGGG-AAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAAGGATTGAG     6
ATAACACAGGG-AAAGGAAGAAAATCCTACCGCCTTTCTGGAGTGACTAACGGAGGCATTGAG     7

GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGGAAAAGGGAAAAGTTGGGAAAAGTA     1
GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGGAAAAGGGAAAAGTTGGGCAAATTG     2
GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGGAAAAGGGAAAAGTTGGGCAAATTG     3
GAAGCGTGCC232AGGCAAGTGGACTTTGGAGGCTCTGGAAAAGGGAAAAGCTGGGCAAATTG     5
GAAGCATACC238AGGCAAATGGACTTTGGAGGCTCCAGAAAAGGGAAAAGCTGAGCAAATTG     6
GAAGCATACC233AGGCAAGCGGACTTTGGAGGCACTGGAAAAGGGAAAAGCTAGGCAAATCA     7

TATGTCTAATAGGGCTTGCTTCCAGTGTGGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA     1
AATGCCTAATAGGGCTTGCTTCCAGTGCAGTCTACAAGGACGCTTTAGAAAAGATTGTCC-AA     2
AATGCCTAA                                                           3
AATGCCTAATAGGGCTTGCTTCCAGTGCGGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA     5
AATGCCTAACAGGGCTTGCTTCTAGTGTGGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA     6
AATGCCTAATAGGGTTTGCTTCCAGTGCGGTCTACAAGGACACTTTAAAAAAGATTGTCCAAA     7

-TAGAAATAAGCCACCACCTCGTCCATGCCCCTTATGTCAAGGGAATCACTGGAAGGCCCACT     1
GTAGAAATAAGCCGCCCC-TCGTCCATGCCCCTTATGTCAAGGGAATCACTGGAAGGCCTACT     2
GTAGAAGTAAGCCGCCCCCTCGTCCATGCCCCTTATTTCAAGGGAATCACTGGAAGGCCCACT     5
GTAGAAACAAGCTGCCCCCTTGTCCATGCCCCTTATGTCAAGGGAATCACTGGAAGGCCCACT     6
-TAGAAATAAGCCGCCCCCTCGTCCATGCACCTCGTGTCAAGGGAATCACTGTAAGGCCCACT     7

GCCCCAGGGGATGAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATGA                    1
GCCCCAGGGGACGAAGGTCCTCTGAGTCAGAAGCCACTAACCTGATGA                    2
GCCCCAGGGGACAAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATGA                    5
GCCCCAGGAGATGAAGGTCCTCTGAGTCAGAAGCCACTAACCAGATAA                    6
GCCCCAGGGGACGTAGGTCCTCTGAGTCAGAAGCCACTAACCAGATGA                    7
```

FIGURE 9.2

```
RTPLSTQTVQKDIDKGVNNEPKSANIPWLCTLQAVGEEFGPARVHVPFSLSHLKQIKIDG   SDSPDG
- = === ===-=== == ======== =  ===== =============  ===== = =  == ===
KDPPSTQMVQKEIDKRVNSEPKSANIPQLPLQAVGGREFGPARVHVPFSLPDLKQIKTDLGKFSDNPDG

YIDVLQGLGQSFDLTWRDIILLLNQTLTSNERSAAITGAREFGNLWYLSQVNDRMTTEERERFPTGQQ
========== ========- ======= =====-==-= ===-================= ======
YIDVLQGLGQFFDLTWRDIMSLLNQTLTPNERSATITAAXEFGDLWYLSQVNDRMTTEEREXFPTGQQ

AVPSVAPHWDTESEHGDWCRRHLLTCVLEGLRKTRK TMNYSMMSTITQGK
====- ============= ================--============-
AVPSLDPHWDTESEHGDWCCRHLLTCVLEGLRKTRKKSMNYSMMSTITQGR
```

FIGURE 10

09/719554

WO 99/67395

PCT/FR99/01513


```
GTCTACCTAGCCA-AGGCATATTCTTCTTATGTGGAACATCAACCTATATCTGCCTCCCCACTAACTGGA
:::: :::: ::  ::: ::::: ::  : ::::: :: ::: :::::    ::  :    : :  ::
GTCTGCCTACCCTCAGGAATATTTTTGTCTGTGGTACCTCAGCCTATCGTTGTTTGA--A-TGGCTCTT
CAGGCACC-TGAACCTTAGTCT--TTCTAAGTCCCAAC-ATTAACATTGCCCCAGGAAATCAGACCC-TA
:::    :  ::   : ::  :::   :::: ::: ::   : :: : :::    : : : : :  :::    ::
CAGAATCTATGTGC-TTCCTCTCATTCTTAGTGCCCCCTATGACCATCTACACTGAACA--AGATTTATA
TTGGTACCTGTCAAAGCTAAAGTCCCGTCAGTGCAGAGCCATACAACTAATATCCCTAT-TTATAGGGTT
  : ::  ::::: : :::: : ::::   :     ::::   :   ::   :   : ::: : : :::::::
CAGTTA--TGTCATATCTAA-GCCCCGCAACAAAAGAGT-ACCCAT-TC-T-TCCTTTTGTTATAGGAGC
AGGAATGGCTAC-TGCTAC-AGGAACTGGAATAGCCGGTTTATCTACTTC-ATT-A-TCCTACTACCATA
:::: :: :::   ::: :: ::: ::::: :: : :::: :   : :: :: : : : : ::::::: : :
AGGAGTG-CTAGGTGC-ACTAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAA-A
CACTCTCAAAGAATTTCTCAGACAGTTTGCAAGAAATAATGAAATCTATTCTTACTTTACAATCCCAA-T
:  :::::: ::: :      :  :  : : : :          ::  ::  :  : :: :: :::   ::: :
CTATCTCAA-GAACTAAATGGGGACATGGAACGGGTCGCCGAC-TCCCTGGTCACCTTGCAAGATCAACT
TAGACTCTTTGGCAGCAAT-GACTCTCCAAAACCGCCGAGGCCCACACCTCCTCACTGCTGAGAAAGGAG
:: ::::  : :::::: : : : :: ::::: ::  :::     : :: : :: :: ::::: : ::: :
TA-ACTCCCTAGCAGCAGTAGTC-CTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGG
GACTCTGCACCTTCTTAGGGGAAGAGTGTTGTTTTTACACTAACCAGTCAGGGATAGT-AC-GAGAT-GC
::  :::     :: ::::::::::: :: :::: :::     ::: :: :: :: :: :: :: ::::  :
GAACCTGTTTATTTTTAGGGGAAGAATGCTGTTATTATGTTAATCAATCCGGAATCGTCACTGAGAAAGT
CACCTGGCATTT-ACAGGAAAGGGCTTCTGATATCAGACAATGCCTTTCAAACTCTTATACCAA---CCT
 :   :  :::  : :   ::    :   :   : : :::: : :: ::  :::: ::    ::     :::
TAAA-GAAATTCGAGATCGAATA-CAACGTAGAGCAGAGGA-GC-TTCGAAACACTGGACCCTGGGGCCT
CTGGAGT---TGGGCAACATGGCTTCTTCCATTTCTAGGTCCCATGGCAGCCATCTTGCTGTTACTCACC
:   ::    :::     : ::: :::: :: ::  :::: ::  : ::::: ::   :  :: :::::  :
CCTCAGCCAATGGATGCCCTGGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTC
TTTGGGCCCTGTATTTTTAAGCTTCTTGTCAAATTTGTTTCCTCTAGGATCGAAGCCATCAAGCTACAGA
::::: :::::::: ::::: :: ::::: :: ::::: :: :: :: ::::::::   :    : :: : :
TTTGGACCCTGTATCTTTAACCTCCTTGTTAACTTTGTCTCTTCCAGAATCGAAGC--T---G-TAAA-A
TGGTCTTACAAATGGAACCCCAAATG-AGTTCAACTAACAACTTCTACCAAGGACCCCTGGAACGATCCA
    :: ::::::::: ::: : ::: ::: :::   :  ::   ::::::    :::::::::: ::  :
----CT-ACAAATGGAGCCCAAGATGCAGTCCAAG-ACTAAGATCTACCGCAGACCCCTGGACCGGCCTG
CTGGC--ACT-TCC-AC-T-A--GCC-T-AGAGATTCCCCTCTGGAAGACA-CTACAACTGCAGGGCCCC
:: ::  ::  ::  :  : :  : : : : ::   ::::::  :: :: : :: :: :::::   :: :
CTAGCCCACGATCTGATGTTAATGACATCAAAGGCACCCCTCCTGAGGAAATCT-CAGCTGCACAACCTC
TTCTTTGCCCCTATCCAGCAGGAAGTAGCTAGAGCGGTCATCGGCCAAATTCCC-AACAGCAGTTGGGGT
: ::  ::::: :: :::::::::: :: :::::::::: ::::::::  :::: ::::::: :: :: :
TACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCCCCAACAGCACTTAGGTT
GTCCTGTTTAGAGGGGGG
 ::::::: ::: :::::
TTCCTGTTGAGATGGGGG
```

FIGURE 11

```
ACCTTGCAAGATCAACTTA-ACTCCCTAGCAGCAGT-AGTCCTTCAAAATCGAAGAGCTTTAGACTTGCT
:: :: :::    ::: : : ::::  : :::::::: : :: : ::::: ::   :::    ::::  : ::
ACTTTACAATCCCAAATAAGACTCTTTGGCAGCAGTGACTC-TCCAAAACCGCTGAGGCCTAGATCTCCT
AACCGCTGAAAGAGGGGGAACCTGTTTATTTTTAGGGGAAGAATGCTGTTATTATGTTAATCAATCCGGA
 :: ::::::: ::: :::  :::     :: ::::::::::: :: :::: :::    ::: :: :: ::
CACTGCTGAAAAAGGAGGACTCTGCACCTTCTTAGGGGAAGAGTGTTGTTTTTACACTAACCAGTCAGGG
ATCGTCACTGAGAAAGTTAAAGAAATTCGAGATCGAATA--CAACGTAGAGCAGAGGAGCTTCGAAACAC
:: : :: :::::  :  :   :   :  : :  ::: :  :  :  : : :::: :   ::: :::  :
ATAG-CA-TGAGAT-GCCACCCAGCGTTTACAG-GAAAAGGCTTCTGAAATCAGACGCCTTTC-AAATTC
TGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCTGGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATA
:    ::     ::::   ::    :::     : ::: :::::::::::  :::: ::  : ::::: ::
TTATACCAA---CCTCTGGAGT---TGGGCAACATGGCTTCTCCCCTTTCTAGGTCCCGTGGCAGCCATC
ATATTGCTACTCCTCTTTGGACCCTGTATCTTTAACCTCCTTGTTAACTTTGTCTCTTCCAGAATCGAAG
 :  :: :::::  :::::: ::: :::: :::::::: ::::: :: ::::: :   :: :::::::: :
TTGCTGTTACTCGCCTTTGGGCCCCGTATTTTTAACCTTCTTGTCAAATTTGTTTGGTCTAGAATCGAGG
C--T---G-TAAA-A----CT-ACAAATGGAGCCCAAGATGCAGTCCAAG-ACTAAGATCTACCGCAGAC
:  :   : :: : :    :: :::::: :: ::: : ::: ::: :::   :  ::  :::::::  :::
CCATCAAGCTACAGATGGTCTTACAAATCGAACCCCAAATG-AGTTCAACTAACAACTTCTACCGAGGAC
CCCTGGACCGGCCTGCTAGCCCACGATCTGATGTTAATGACATCAAAG-GCACCCCTCCTGA-GGAAATC
:::::::: : :: ::: ::  ::  ::   ::     : : : : :: :  ::::: ::: ::: : :
CCCTGGACTGACCAGCTGGC--ACT-TCCCCTG-----GCC-T-AGAGAGTTCCCCTC-TGAAGGACA-C
T-CAGCTGCACAACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCC
: :: ::::: : :: :: :: :::::: :: :::::::::: :: :::::: ::: ::::::::  :::
TACAACTGCAAAGCCCCTTCTTCGCCCCTATCCAGCAGGAAGTAGCTAGAGCAGTCATCGGCCAAATTCC
CCAACAGCACTTAGGTTTTCCTGTTGAGATGGGGG
: ::::::: :: :: : :::::::::  :: :::
C-AACAGCAGTTGGGGTGTCCTGTTGAT-TGAGGG
```

FIGURE 12

```
agttgcaattccttgcctcaactctgagagaaaccccagccacatctccagcaaacaaga
agttgcaattccttgcctccactgtgagacaaaccccagacacatctccagcacacaaga 2299

acttcaaaacacctgaactgcagcagccaggcgttcctccaggaccacctcccccaggat
acttcgaaatgcctcaacctcaggtgccaggggttcctccagaaccttctcccccaggag 2359

cttgcttcaagtgccggaaatctgaccattgggccaaggaatgcctgcagcccaggattc
cttgctacaagtgccagaaatctggccactgggccaaggaatgcccacagaccaggattc 2419

ctcctaagccacgtcccatttgtgcaggaccccactggaaatcggactgtccaactcacc
ctcctaagctgtatcccatctctgtgggaccccactaaaaatcagactgttcaactcacc 2479

cggcagccaatcccagagcccctggaactctggcccaaggctctctgactgactccttcc
tggcagccacttccagagcccctggaactctagcccaaggctctctgactgaccccttct 2539

cagatcttctcggcttagcagctgaagactgacactgcccgatcacttcagaagtcccct
gagatcttcttggcttagcagctgaagactgacactgccagatcgcctcggaagcctaca 2599

ggaccatcacggatactgagcttcaggtaactctcacagtggaggctaagtccatcccct
ggaccatcacagat-----gctccaggtaactctcacagtagagggtaagtctgtcccct 2654

gtttaatcgatacaggggctacccactccacatcaccttcttttcaagggcctgtttccc
tcttaatcaatatggaggctacccactgcacattaccttcttttcaagggcctgtttcct 2714

tttcccccataactgttgtgggtattgacggccaagcttcaaaaccccttaaaactcccc
ttgcctccataactgttgtgggtattgacggccaggcttctaaacctcttaaaactcccc 2774

cactctggtgccaacttggacaacattcttttatgcactctttttcagttatcctcacct
aactctagtaccaacttagacaatactcttttaagcactccttttagttatccccactt 2834

gcccagttcccttattaggccgagacatttaaccaaattatctgcttccccgactattc
gcccagttcccttatgaggccgagacacttcaactaaattatctgcttccctgactattc 2894

ctgggctacagccacatctccttgccgcccttcttcccaacccaaagcctccttcatatc
ctggactacagctacatctcattgctgcccttcttcccaatccaaagcctcctttgcatc 2954

ttcctctcatatccccccaccttaacccacaagtatgggacacctctactccctccctgg
ttcttgt---atcccccaaccttaacccacaagtataagatacctctattccctccttgg 3011
```

FIGURE 13.1

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```
caaccgatcacacgcccattactatcccattaaaacctaatcacccttaccctgctcaat
tgaccaatcatgcaccccttaccatctcattaaaacctaatcactcttacccggctcaat 3071

gccagtatcccataccacaacaggctttaaagggattgaagcctgttatcacttgcctgc
gccaagatcccatcccacagcatgctttaaaaggattaaaacctgttatcactcgcctgc 3131

tacagcacgggcttctaaaacctataaactctccatacaattcccccatttacctgtct
tagagcatggcctttaaagcctataaactctccttacaattcccccatttacctgtcc 3191

aaaaaccagataagtcttacaggttagttcagaatctgcaccttatcaaccaaattgttt
tagaaccagacaagccttacaggtt----caggatctgtgtcttatcaatgaaattgttt 3247

tgcctatccaccctgtagcacccaactcgtacactcttttgtcctcaatgccttcccca
tccctatccaccctgtggtgctgaacccatatactctcctatcctcaatacctccctcta 3307

caactcactattccgttcttgatcttaaagatgctttttcactattcccctgcacccct
caacccattattctgttctagatctcaaacatgctttctttactatccctttacaccctt 3367

catcccagcctctctttgcttttacctggactgaccctgacacccatcagtcccagcagc
caacccagcctctcttcgttttcacctggactgaccctgacacccatcagtcccagcagc 3427

ttacctgggctgtactgccgcaaggcttcagggacagccctcattacttcagccaagctc
ttacctgggctgtaatgctgcaaggtttcaggggcagcccttattatttcagccaagctc 3487

tttctcatgatttactttctttccacctctctgcttctcaccttattcaatatattgatg
tttctcatgatttactttctttccacccctccacttctcaccttattcaatatattggtg 3547

accttctactttgtagcccctcctttaaatcttctcaacaagacaccctcctgctccttc
atgttcttctttgtagcccctcctttgaatcttctcaacaagacacacttctgctccttc 3607

aacatttgttctccaaaggatatcgggtatccccctccaaagctcaaatttcttctccat
agcatttattctccaaaggatatc-------cccctccaaagctcaaatgtcttctccat 3660

ctgttacatacctcggcataattcttcatgaaaacacatgtgctctccctgccaattgcg
ccgttacctaccttggcataattcttcataaaaacacacgtgccctccctgctgatagtg 3720

tctccaactgatctctcaaatcccaacctcttctacaaaacaacaactcctttccctcct
tctg--actgatctctcaaaccccaaccccttctacaaaacaacaactcttttccatcct 3778

aggcatggttggatacttttgcctttggatacctggttttgccatcctaacaaaatcatt
aggcatggttggatactttcgtgttaggatacctggttttgccatcctaacaaaaccatt 3838
```

FIGURE 13.2

```
atataaactcacaaaaggaaacctagctgaccccatagattctaaatcctttccccactc
|||||||||||||||||||||||||| ||||||||||||| ||||||| |||||||||||
atataaactcacaaaaggaaacctagttgaccccatagatcctaaatcgtttccccactc 3898

ctctttccattccttgaagacagctttagagactgctcccacactagctctccctgtctc
|||||||||||||||||||||||||||||||||||   |||| ||||||||||||| |||
ctctttccattccttgaagacagctttagagactgtctccactctagctctccctgactc 3958

atcccaacccttttcattacacacagccgaagtgcagggctgtgcagtcggaattcttac
|||||||| |||||||||||||||||| ||||||||||||||||||||| ||||||||||
atcccaacacttttcattacacacagctgaagtgcagggctgtgcagtcagaattcttac 4018

acaaggaccgggaccatgccctgtagcctttttgtccaaacaacttgaccttactgtttt
||||||||||||| |    |||||||||||||||||||||||||||||||||||||||||
acaaggaccgggatcgcatcctgtagcctttttgtccaaacaacttgaccttactgtttt 4078

aggctcgccatcatgtctccatgcggtagcttccgctgccctaatacttttagaggccct
||||| |||||||||||||||||| |   || | ||  ||||||||||||||||||||||
aggctggccatcatgtctccatgcagcgtctgctgccaccctaatacttttagaggccct 4138

caaaatcacaaactatgctcaactcactctctacagctctcacaacttccaaaatctatt
||||||||||||||||||||||||||| |||||||||||||| || ||||||||||||||
caaaatcacaaactatgctcaactcattctctacagctctcataatttccaaaatctatt 4198

ttctttctcacacctgacgcatatactttctgctccccggctccttcagctgtattcact
||||| |||||||||||| |||||||||||||||||||||||||||||| | || |||||
ttcttcctcacacctgacacatatactttctgctccccggctccttcagatatactcact 4258

ctttgttgagtctcccacaattaccattcttcctggcccagacttcaatctggcctccca
|    || | |||||||||||||||||| ||||||||  |||||||||| |||||||||
c--catttattctcccacaattaccattattcctggcctggacttcaatccggcctccca 4316

cattattctggataccacacctgaccctgatgattgtatgtctctgatctacctgacatt
||||||||||||||||| |||||||||| |||| || || ||||||||| ||||||| ||
cattattctggataccatacctgaccctcatgactgcatctctctgatccacctgacgtt 4376

caccccatttccccatatttccttcttttctgttcctcatgttgatcacatttggtttac
||||||||||||||| ||||||||||   ||||| ||||  |||||||| ||||||||
caccccatttccccacatttccttctgccctgtttctcaccctgatcacacttggtttat 4436

tgacggcagttccaccaggcctgatcgccactcaccagcaaaggcaggctatgctat
||| |||||||||||||||||| ||||||||||||||||||||||||| ||||||||
tgatggcagttccaccaggcctaatcgccactcaccagcaaaggcaggatatgctat 4493

gaactgattgccttaactcgggccttcactcttgcaaagggactacacgtcaatatttat
|||||  ||||||||| ||  ||| ||||||||||||| |||||||  |||||||| |||
gaactagttgccttaattcaagccctcactcttgcaaaaggactacgtgtcaatatctat 4553

actgactctaaatatgccttccatatcttgcaccaccatgctgttatatgggctgaaaga
||||| |||||||||||||| |||||  ||||||||||||| || |||||||||||||||
actgattctaaatatgcctttcatattctgcaccaccatgcggtcatatgggctgaaaga 4613

ggtttcctcactacgcaagggtcctccatcattaatgcctctttaataaaaactcttctc
|||||||||||||| |||| |||||||||||||||||||||||||| |||| |||| |||
ggtttcctcactacacaagtgtcctccatcattaatgcctctttaagaaaa-ctctgctc 4672
```

FIGURE 13.3

```
aaggctgctttacttccaaaggaagctggagtcacacactgcaagggccaccaaaaggcg
||||||||||||||||||||||||||||| ||||  ||||||||||| || |||||| | 
aaggctgctttacttccaaaggaagctggggtcattcactgcaaggggcatcaaaagact 4732

tcagatcccattactctaggaaatgcttatgctgataaggtagctaaagaagcacctagc
|||||||||||| ||||||| |||||||||||||||||||| |||| | ||||| |||||
tcagatcccattgctctaggcaatgcttatgctgataaggtggctagacaagcagctagc 4792

gttccaacttctgtccctcatggccagtttttctccttcccatcagtcattcccacctac
 ||||||||| |||||||||||||||||||||||||||| |||| |||| ||||||||||
tctccaactttgtccctcatggccagtttttctccttcacatccgtcactcccacctac 4852

tcccccattgaaacttccgcctatcaatctcttctcacacaaggcaaatggttcttagac
||| |   |||||||||| |||||||| |||||| | | ||||| |||||||||||||||
tccacagctgaaacttccacctatcaagctcttcccccgcaaggtaaatggttcttagac 4912

caaggaaaatatctccttccagcctcacaggcccattctattctgtcatcatttcataac
||||||||||||||||||||||||||||||||||||||||||||||| ||||||||||||
caaggaaaatatctccttccagcctcacaggcccattctattctgtcgtcatttcataac 4972

ctcttccatgtaggttacaagccactagtccacctcttagaacctctcatttcctt-cca
|| ||||||||||||||||||||||||| |   ||||||| ||||||||||||||| |||
cttttccatgtaggttacaagccactagcctgtctcttaggacctctcatttcctttcca 5032

tcgtggaaacatatcctcaaggaaatcacttctcagtgttccatctgctattctactacc
|| ||||||  |||||||||||| |||||||||||||||||||||||||||||| |||||
tcatggaaatctatcctcaaggagatcacttctcagtgttccatctgctattctgctacc 5092

cctcagggattgttcaggccccctcccctccctacacatcaagctcggggatttgcccct
|||||||||||||||||||| |||||| | ||||||||| ||||||||||||||||||||
cctcagggattgttcaggcctcctccctttcctacacataaagctcggggatttgcccct 5152

gcccaggactggcaaattgactttactcacatgccctgagtcaggaaactaaaatacctc
|||||||||||||||||||||||||||||||||||  | ||||| ||||||||||| |||
gcccaggactggcaaattgactttactcacatgcctcgggtcagaaaactaaaatatctc 5212

ttggtctgggtagacactgtcactggatgggtagaggcctttcccacagggtctgagaag
|| ||||||||||||||| ||||||| ||||||||||||||||||| || ||||||||||
ttagtctgggtagacactttcactgggtgggtagaggcctttcccatagagtctgagaag 5272

gccactgcagtcatttcttcccttctgtcagacataattccttgggttggccttcccacc
||||| || |||||||||||||||||||||||||||||||||||| |||||||||||  |
gccaccgcggtcatttcttcccttctgtcagacataattccttggtttggccttcccttc 5332

tctatacagtccaataacggagcagcctttattagtcaaatcacctgagcagtttttcag
|||||||||||  |||||||| ||||||||| ||| |||||||||  |||||||| ||||
tctatacagtctgataacggaccagcctttactagttaaatcacccaagcagtttctcag 5392

gctcttggtattcagtggaaccttcgtaccccttactgtcctcaatcttcaggaaaggta
||||||||||||||||||||||||| || ||||||   ||||||||||||||||||||||
gctcttggtattcagtggaaccttcatatcccttaacatcctcaatcttcaggaaaggta 5452

gaatggactaatggtcttttaaaaacacaccccaccaaactcagcctccaacttaaaaag
 ||  |||||||||||||||||| ||||||| |||||| |||||||||||||||||||||
aaaccgactaatggtcttttaaagacacacctcaccaagctcagcctccaacttaaaaag 5512
```

FIGURE 13.4

TGCCTTTATTTCCGTAGGCTGGTCATATGGCGCTAGCACTCACATAAAGCTACCGAGGAG
AGCGAATGAAACCAAAATCACTTTACCTTCACAGCACGAGGCCGTCGTCCCTCTCGATAT
TTGGCCCGTGTGTCGCATACCGCCCTCTGGACGTGGTGATCAAATAAACTCCCTAGCTCC
CCGCCGCTCGACGCCATCTTGCCTACTTTGATCCTCGCAGGGAGGACAACATCCGCCCTA
CTGAGCTCCCTTTTATCCAATAAGAGAGCGGGATGAGTTAAGGAGTGCCAGGATTGGCTG
GAGAATCGACAGCGTCGGCCATCGTTTCCTGCGTGCGAAGATTTGATGAACGAGGTGCCG
CCCCCGAGCGGCTCGGCGGAGAGGCGCGGTGGGTGACAGAAGCTTTCTTGTCCCACCCAC
TACAGGCTTACGGCAGGATGCGCAGCGGGGAGAGGGGGCGGGGCCGCAGGGGGCGGGGCC
GATCGATCTCCTCCGGCTCCGACGTCCTCGGCCTGCCGGGTCCCGGGTCCTTTGCGGCGC
TAGGGTGGGCGAACCCAGAGCGACGCTCCGGGACGATGTGGGGCAGCGATCGCCTGGCGG
GTGCTGGGGGAGGCGGGGCGGCAGTGACTGTGGCCTTCACCAACGCTCGCGACTGCTTCC
TCCACCTGCCGCGGCGTCTCGTGGCCCAGCTGCATCTGCTGCAGGTAACCTGCCGGCCCC
GAGCCACCTGATCTTCAGCCTGGGGTCGGACGAGGCCGAAGCCTCTCAGGGACGCGGCGG
GACACCGGCTGCCACCCGGGCGCCGCCGAAGCGCGCAGAGATCAGGGTCCCTCGACGGCA
GGGCCCTTCTGGGTAGTCTCTGGATCCCACAAGTCCAGTGCAGCCCTGGGCTCGTCTTAT
CCCAGGTCTTTTCACTTGGTGAAACTGAACCTAGAAACGTCCTAATATTCTACCACTGTT
TTTATAAATATTCCTTATTCCAGGCTGGAAAAGCTCCTGAGAAGTGGTTTGTTTTTATTA
TTTTAAAAGGTGTTTTCCTTGCCAGCCATTTCCAGTTAACCTGCGCTGCTGCCGTCCGGG
CCGCGAGAGCGGGACGCAGAGTTGTTGGCGGAGCCCCTGTCGGTTCCCGGGGACTAAGCA
CCGCGTCCCATGAGCGGGAAAGGTTAATACAATGATGGTTCTGCCCTGCGTCGCTGACGC
GGAACACAGCTGTAGTGTGTTAGGAACACATAACGTAGTTAAGATCACTTGAAGCTCTGC
GATCAGTCGCCCTTCTGGACGTTGTGGTTAGGATGTTTCACAGTTCTAACCACTGGTGGA
GATACAGCGTCCATATTTTCATAATTAAAAATAGAGGCACATGGTCTCACGAGTTTGAGT
GTACTTATGGGGGCAAAAGGACGGCGTATTTGAAATCCTCATAAATCCTGGATGCATGGT
ACCCACCAGTGGCTAATCTATGCAATGAATAGAGTTTGCAATAATTTCAAGCATCCCTTC
TTTCCACTTGAGTTACTTCCCCATACCTAGGGGAAGATATTTTTGGTCCACTGAAAACAT
GAGTTCAGCAGAATCCTCCTATCATCGTCGTTATTATTTTTTACCACTAAGTAGACAATC
TTTTGGTTTTTGATGGGCTTTATGGCTAGAGACAAATCAGTCACTGTCACCAAGTTCCAG
GTAGAAGTTGGTTCAGTGCTCTGTCAGCTTCGATGGGATTTTTCAACATGTTTTCAAATC
TGCACTTAATAGTAGGAATGCTTTCTTACAGTAACTCTAATTTGATCCTAAGATGTAGTT
GTTACCTTACATTCATCACTGTTTAAGAATTTAGTGGTCTTGATCTTTGTTTTAAATTTT
GAGCCTTCGGGAAGTACTTATAAGAATTAATTCATGCATATCTTTTTGAAATGTAAATGT
CTTTAGCCCTGGAACAAATTGCTGTTTCTGTTCAGCCCATATTAGCAGAATAGGTCAACT
TTACTTTCTAATTATCAATGTAATAAGTTTATTACTTTATAGATTCCATAAATCTATACA
TTTATTCCTCGATGAATTATATAAATTTATAGAATTTATGTTTTATAGAAAATTTGGAAA
GCATGGAAAATTATTAACAAGAAAATAAGTTACCCATAATCCCAGAACTTAGAGGTGACT
AATGTTGACAGTTTGGATCAAATCTTCCAGTTTTGTTTCTAATCTTTATTTTTAACATAA
ATGAGGTCCTGTATACACACGTACAGTTTTGTGTCCTGGTGTTTTTATTTAATGTTATTA
TGAGTGTTTTATTTTGTTAAAAGGTCATCATTTTAAGTTGTTAATTAGTATTCTAGCACA
AATTTGCCATAATTTATTTAATTGTTTACTATGATTGACCATTTAGATTGTACTTAATTT
TTAGGCATTAGAAGTGATAAACTATATTTTAATCAGACGTTGAAAATAACACATCTTTGT
TTAGAAAACATCATTTTATTTCTGGTTGTCTAGGATAGATTCCCAGAATTCTTGGGTTAG
AGGCCATAGATAATTATGAAAGCAGAAAGATTCACAAGTTGGGAGTTAATACTTGAATTA
CTTTATTTGGGGTGAAGCATTGAGTGCATAATACAGATCATGCAGTAATGGAAGAAGGG
TTGGAACAATGGTTTTCTGGCCTATGTCAGACTTACCTTGAAGCTTTTAAGAATACAGAT
GTTCTGATCAACCCTCAGACCTATTAAATCAGACCTAAAATCTTAGGGAATAGGCTTTAG
GCATCTCTAATTTTAAAAAATTTATTCAGGCTACTTGGATGCACAAAAGAGTTGAGACCT
ACTGTCCTAGAATCATAGAATTTTAATGACGATAGAGACCTTAAGCATCTAGGTCGTTTC
TGTACTTTTACATGTAAGGAAACTGGCATTCCTAGGCCAGTACCATTGCCATGCAGCTAA
TTTGCCCTCTTGTCTATAGCTCACTCTGCATCACCCAACCTACCGTTCTCACTGTTTCTT
CTATAACCAATCTCCTTCCCACTTCTGTTCTCTTACTCATGCCATTCTTCCCTCAGTCAT
TTTTCTTCCTTCCATACAAATTCCATGTCTTTAAAAAGGAATAATCCTACCTCCTCCACA

FIGURE 14.1

TAGCTTTCCAATTCTCTGTTGCCCACATTTGTCTCCCTTTCAATACTTCTCTGTTGTGTT
ATGTGACACATCACATTTGATATACTCTGTACTGTGTTTCAAGTATTGTATTCTCTTGTT
TACTCAAGTCATTATTTCAGGACTGACTACCCAGTAGATGCTTTAAGTCAGGATTTCTCA
ACCTTGGCACTGTTGACATTTTGAGCTGGATAATTTTTTGTTTTGGGGGCTCTCCTGTAC
ATTTTAAGATGTTTAACAGCACCCTTGGCCTCTATCCAGTAGACGCCTGTACTGCCTCCC
CCTATCTGTGACAACCAAAAAGGTCTTCAGACATTGTCAGATGTCTACTGAAGGACAAAA
TCACCTCTGGTTGAGAACCACCGCTTCAACTAAGTTATCTTCTCTGTACTCAGAACTTGA
TGTGATTGCAGCAGGGGGAGAGGATTCATATACACAGTGAATGCAAACGAACCTAAATCA
CCATTCGGATATGGCCACACAATTTTCATTTCCCTTGTGTTAGCAAGAGATACCCTAGGC
TTTGGACCTGATTATTCCTAAGGCATTCTGATGTATGGTTTTACCTGCAGATTTCCTGGT
AATACTGATACCTCAGTTTGGGTCAAAGAAGGTCAATTAATTGATTGATTTGATTTGACT
CCTGGAAAAGACGCTCCTTTCTAGCTGTCTCTTTCTTCTCTTTACCTGAATAGCCAGGGC
TCTGTGGTTCAAGTGAAGTATTTTGACATAAAAATTAACTTAGAACATTGGTCTGCAGAG
TTTGCTCAATATAACTGAGCACATATTGTGGCTTTATGGAGCTGGTTACTACTTTTTGAC
CAAATAAATAATTAGAAGTATTTTTCCTCCTCAATAAGGTTCATTTTTCCTTTTTTCAGT
GAGCTGGTAGAGTTTCCTTTTTTGATATTTCAGGGCATCTTTCATATTTCCATCTCTTAA
GTTTCTTCATATGAAGTAGAATTTATCTGGATTATGTATTGCTGACTCTGATGAAAACCC
ATAGAAAGCATCTGGGGCTTGATCACCTTCATTCTTGTAATAGCTCACACGGTTACAGCT
GATATGGTAACTTAAGACTTTTGATTCCAAATCTAGGCAAAATACACTCAGTTGAAAGAA
TTTGTCAGCCAGAACAGTTGGACTGTTCTGTGAAAATTGTGAGAAAAAATTACACAACTAA
GTGATACATGATGATGGCTTTCTTAAATATAAAATTGTAATAACATGGTTAATTTCCAGT
ACGTTATATTGTCCCAGAAGTGGCTCCAACATTGTTTGAAATTTGTCTCATTTAAAGAAA
CATAAGCTGGCTATGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCAGG
CAGATCACCTGAGGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTAAAACCCCATCTC
TACTAAAAATACAAAAATTAGCCGGGCATTTGGTGGGGGCCTGTAATCCCAGCTACTTGG
GAGGCTGAGGCAGGAGAATTGCTTGAATCTGGGAGGTGGAGGTTGCAGTGAGCCGAGATT
GTGCCACTGCCCTCCAGCCTGGGTGACAGAGTGAGTCTCCGTCTCAAGAAAAAAAAAAAA
AAAAGCAAGAAACATAAAGACTGGGCATGTTGGCTCATGCCTGTAATCCCAGCACTTTGA
GAGACTGAGGTGGGAAGATCACTTGAGCCCAGGAGGTTAAGGCTGCAGTGAGCCGTGATT
TTGCCACTGTACTCGAGCCTGGGCAACACAGTGAGATCCTGTCTCAGGAAAAAAAAAATT
GCATGTAAATGAATGAATTTGATATTTAATATTTTAAATTATGAAAACTGTTCTGTAGAG
ATGTAGATCTTGCCATGTTGCCCAGGCTGGCTTTGAACTTCTGGGCTCAAACAATCCTCC
TGTCTCAGTCTCCCAAAGTATAAAGATTACACATGTGAGCCACTGCACCTGGCCTAATAT
TTTTAACTTAATGAATTTATTTTGATATAAATAAATTAATAACACTGAAGCTTCCTGATA
TAATAAGTCTTTTTGTGTGTGTGACGGGTTCTCACTCTGTTGCCCAGACTGGAGTGTAAT
GGCACTATCATGGCTCACTGTAGCCTCAACCTCCCTGACTCAAGTGATCCTCCCACCTCG
GCTTCCTGAGTAGATGGGACCACAGGCGTATGCCACCACACCTGGCTGATTTTTAAAATT
TATTATTGATACATATTAATAAAATTATTTTTATTTTAAAAATGATATATGTGGCTGGGC
ATGGTGGCTCATGCCTGTAATCCCGACAGTTTGGGAGGCCGAGGTGGGAGGATCACTTGA
GACCAGGAGCTTAAGACCAGCCTAAGCAACATAGTGAGATCCCATCTCTATAGAAAAAAA
AAATGGCTAGGTGTGGTGGTGTATGCCTATATTCCCAGCTACTCAGGAGACTGAGGTGAG
AGGATTGCTAGAGCCCAGGAGTTTCAAGTTACAGTGACCTATGATTGTGCCAGTGCACTC
CAGCCTGGGCAACAGAGCAAAATCCTGTCTCAAAAAAAAAAAAAAAGTTCGAAAATGCTTAT
GATGCAATATAAGTAGTGGAAAAGGATATTAAATTGTGCCTATATGAACACAACTATATG
AAAAACTTGCACATAGAGAAAAGGATTAACAAGAAATAGACCAAATTGTTCACATGGTTG
TCTTGTTTGTGGAGAGAATATCAGTAGTTCATTTGTTTCCTTCCAAGTTTATATGTTTTC
CGAGGTCTCTATAATGAGTTTGTAATTGTTTAATCATAGAAAACCCTTTTTTGGTCCTTG
GCCACAAACTTACATGTTTTAATGTAATTGCTTTTTTAATGAGAATAAATGTTATATTTT
GCTTTTTTAAAACCTATATTCCCATAGTTATATGAGCCCTTACAATTATTAAGAGGCTGC
ATAATATAACGTTTCTGGAAGGGTACAGAAGAAACAGCAGTAATTACCTCTGAGAACAGA
GACATGGCTTCACATTTTACCCTTTTGTACGTTTTGTGCTTTTGCCACATGCATTTATTA
TTCTTCCAATAAATAAGTAAATAAATATGGATTGTATACTCCATCTGGTTGGTGTTTCAT
AATTCTAAAATTATATTGCTACATTTTTAAAGATGATATGTGTTTCTACTTATTAACGTA

FIGURE 14.2

TATGTTAAAATAGTAAATTTATATCTTATTTAATAATTTCCCTATTGATAGACATTTAAG
ACAGTCTCAAGTGTTCACTATCATAGAAAATACTGCACAGATAGCTTTTGCTATAGTTTC
TTTTTTCTTTGAATCGTTAATTGGGAATAAATGCTCAAATAGTTATATGTGGCTCAACTG
CTATTTAAGTTTATTGACTGACTGCTGCCATTTTGAATTCTGAAGGGGTTGATTAAATTT
ATAATGCTGCCATAAGAATATAAGGGTATTGGCTTCATTAGCATCCACCAGCATTGGGTG
TTGGAAATGATTATAGATTTTTAAATGCTACAACAAATGTAGATAACAGAGAACTATCTA
TAGAACTCTTTTTGGACATGTGAATTGTAATAATAGTTTATTTTCATGTGAATCCAGAAA
AATGTATACGAAAACCTTTTTTCCTCTCATTTCTTATATGAATAGAATCAAGCTATAGAA
GTGGTCTGGAGTCACCAGCCTGCATTCTTGAGCTGGGTGGAAGGCAGGCATTTTAGTGAT
GGGGGACAGGTAAGCACATGTGATGGCAATAACTTTCTTCTAATATCACATAATATAGCA
ATAGAAATAAAATTAAAAGTTTAGATTTTTTGTTAAAGGAGGTGAGATGTCACCTAATTT
GTATGCTATTATGTAACTAGTCTAGGATATTGAAGCTGACTATACTCTGTTTTTAGGTCA
TTATCTTGTAGTTTACCATACTCCCTACTTGCTTCTTATTCTACTATTTAACTCATTTTC
CACATCCCCTAATTTTGGTTTCATGAAATTATTTTTCCTTCTGAATTACTAGGTTCTACT
TACTATTATTAAACTTTATTTCTGACATATTTTATAACCTTCCATGGTCTCACTTGATTA
AAAATAAAAAATTCAGCTGGGTGCGGTGGCTCACACCTATAATCCCAGCACTTTGGGAGG
CCAAGGTGGGCGGATAATTTGAGGTCAGGAGTTGGAGACCAGCCTGCCCAACGTGGTGAA
ACCCCCCCTCTCTACTAAAAATTCAAAAATTAGCTGGGCATGGTGGCAGGTGCCTGTAAT
CCCAGCTACTCAGGAGGCTGAGGCAGGAGAATTGCTTGAACCTGGGAGGTGGAGGTTGCA
GTGAGCTGAGATTGCACTGCTGCACTTCAGCTGGGTGACAAGAGCGAAACAATGTCTTGA
AAAAAAATAAAAAATAAAAAATTCTACAACACAGGGTTATTATTTTTCCATTTTTGTTTT
CCCTTATGAGTTTAATATGTTTAGATTATAAACCTGAAAGCTTGAATACCTATGTCTATC
TTTTGTTTTCTTATGTTTATCAAGTTATTCCTTTAAACATTTTCTAAACTGTAAGAATAA
TGTGAGGCTGGGCTCAATGGCTTATGCCTGTAATCCCAGTGCTTTGGGAGGCCAAGGTGG
GAGGACCACTTGAGGCCACGAGTTCAAGATTAGCCTGGCTAGGCAACATAGCAAGACCCT
ATCTCTATAAAAAAATTAAAAAAATTAGCTGGGCATGGTAGCAAATGCTTGTAGTCCCAG
CTACTCAGCAGACTGAGGTAGGAGGAATGCTTGAGACCAGGAATTTGAGTGACCTATGAT
TATGCACTCCAGCCCGGGCAATAGCAAGACCCTATCTCTTAAAAGAAGAAGATGTAGTAA
TAATACATATTCATTATAACTATTTTACCATTGAAAGTAAAAAATGAGTTTTTACCTTTT
CCCAGTCCCATCCTCAGAATGGGGATCTCAGTAGACCTTTAGGATTGGAAGAATGAGATC
ATTCATATTTTCTGCAATTATTACCCCACAAAATATTTCAGATACCTTTCCATGTATTAC
AAACAATGTGCATTTAACATGTCTCTCTCTTTCTCTCTCTCTCTGTGTGCGTCTTCATGA
TCCTCTGTTGCAGCCCTGCCAGTAAGACACTATCTCCTGAAGAATCACTGATAGGAACAG
AAAGTGGACTGGCTAGGCCAGGAGTCCTTAGCTTCTTAGGGGGCAGGAGCTGCTTTGTGC
TTTCTCAGAATCAGATATATATGTGGACTGAAACATTTAAAAACAGAATAGCCAAGGGTG
CTATACGTTTAAAACTTATATAGATGGGGCTACATTGCTCTCTATTACTAATTTCCCATG
ACAATACACGAGAGTGCCATGTCTTTTTAACTTGTTTTGAGCACAGACTAATCTTGTTTA
TGCATGTTTTTTGATGAGAATAGGCTACTCATGAGAAATCTGTAAACCTAACACTAGTCC
CTTGCATACTCTAAATTGTTGCTAGAATCTTAAAATTTTAGCACCAGACGGACCTTAGAA
ATCATTAACTTTGGTGCTTTGTTCTACAATACAAGGAGATGGAATATTTTACCCAGGATT
GCTTAGCAGGTTACAGTTCTGCCCTCTGAGTACCCAGCACTTCCCTGTGGGCAACATCAA
CTTCCTGATTTTCAAGTCTTAATTAGTACTCTGAAGAATCCTACTTGTTTTTAACTCCCA
TTTGCTTTGAAGTGACTTTACCTGATTTTTTTAGATCCCTTATTGCAGCAATGCCACTAA
GAAACTGAGTCTCTAGCTTCTTGGTGGGCAGGAGCTGCTTTGTGCTTGCTCAGAATCATC
CTTTTCAGTAAGGGAGATATTGAAGAGAAATCTACTGAGGAGTCTGGGGGTGAGGCACTC
AGGGAAATCCTGCTCCAGTCCACAAAAGCAGAGAGGAAGGGTTGGTTACCTAGAGTATTT
AACATGCAGAGGCTTTGGATTTTACTCCTTTAATCCTTGGAAATGCCTATGGAAGGGGAA
AGGAAGTAAGATGGTGACTCCAGCTTATAGACATACTAGTGTTACATATATTTAAACTAT
AATAGGAGGGTATTATTAGTTTTACTTAACTTTCAACTGTGAAGGATTATACTTCTCAAT
ATTTGTCTCCAGTGTCTATTTCAGTGTATTTTTCACTTTTCTTGAAGCAGCATGTCTGTT
GCAAAACTTCTAGAAATAATGAGAATATTTATATATTAGATCAAGCCATAACTTGATGAT
ATAGTCATTTCTTCTTATATTTTTACTTACATTTTTACATTTTAATGATTACTTTCATT
TTTGAAAAACATGTCATGCTGAGATGTATTTTTCTTCATTCTGTAATTAGTTATGAAACA

FIGURE 14.3

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GTTTTTCCTAAAATGCTGAGTATATCAAGTCTTGGCTAAGAATAAGTAATAAATATTTGC
CACATGAAAGACTACACATATAGCCAGGTGCAGTGGCTTGCACCTGTTTTCCCAGCTACC
CAGGAGGCTGAGGCAGGAGGATTGCTTGAGCCCAGGGTTTCCAGGCTGCAGTGAACTATG
ATTGTACCACTCTACTCCAGAATGGGTGACAGAGCCAGGCCCCATCTCTCAAAACAGAAA
AGAAAGATTACATAGACTACATATACACCCCCATCCAAAACATACACACACATCTACTTA
ACCTAAAATGGTAAGAAGATAACTTCTTATTTTCTAATATATGACACAGAAAAGTTTTTT
TAAAGTAGTTTTAAATTTTTAATTTTTTCTAGGTATTTCTCAAGCCATGTTCCCATGTGG
TATCTTGTCAACAAGTTGAGGTGGAACCCCTCTCAGCAGATGATTGGGAGATACTGGTAA
AGAAAACCAAATAAGAACTATCTCATTTAAGGTTAAATTACTTCACAATATCAATGTCTT
TAGCTTTCTCTAAGCTTTATTATATATTCTGAGTTGGTTTTGAATTATAAGAATGAATTG
GGGCCAGGCACAGTAGCTCATGCCTATAGTCCCAGCACTTTGGGAGGCCAAGGCAGGTGG
ATTGCTTGAGTCCAGGAGTTCAAGACCAGGCTGGGCAACATGGTGAAACCCCGTATCTAC
TAAAAATACAAAAATTAGCCAGGCATGGTAGTGCATGCCATTAGTCCCAGTCACTTGGGA
GGCTGAGGCAGGAGAATCGCTTGAGCCCGTAAAGTCAAGGCTGCAGTGAGTCAGGATCTT
GCCATTGTACTCCAGTCTGGAAAACAGAGTGAGACCTTGTCTCAAATAAAAAAAGAATGA
ATTGATAGAGATCTAATGTACAACCTGACAACTATAGGTAATAAAATTGTATTGGGGATT
CATGTTAAATGAGTAGATTTTAACTACTCTTACCACAAAAACACAAAAGTGGGTAACTGT
GAGATGATGTATATGTTAATTTACTTCACTATAGTAACCATTATACTATCTATATGTAGC
TCATAACACCATGTCGTGTATATTAAATATGCACATTAAAATTTGTTTTTTAAAAAAAGA
ATTGAGATTTTTTTTAACTAGATATGGAGTGGACAAAATGTAAAGTGAATTGATCTTTTC
GTCTGTTGGTTCTAGGAGCTGCATGCTGTTTCCCTTGAACAACATCTTCTAGATCAAATT
CGAATAGTTTTTCCAAAAGCCATTTTTCCTGTTTGGGTTGATCAACAAACGTACATATTT
ATCCAAATTGGTAGGTGCTATTGTAATATTTGCTGTCATATTCTACACTATAGCATTGAG
TCCAAAGTAGAAATGAATGTGCACTAATGAGCTTTATTTTCTACACAGTTGCACTAATAC
CAGCTGCCTCTTATGGAAGGCTGGAAACTGACACCAAACTCCTTATTCAGCCAAAGACAC
GCCGAGCCAAAGAGAATACATTTTCAAAAGCTGATGCTGAATATAAAAAACTTCATAGTT
ATGGAAGAGACCAGAAAGGAATGATGAAAGAACTTCAAACCAAGCAACTTCAGTCAAATA
CTGTGGGAATCACTGAATCTAATGAAAACGAGTCAGAGATTCCAGTTGACTCATCATCAG
TAGCAAGTTTATGGACTATGATAGGAAGCATTTTTTCCTTTCAATCTGAGAAGAAACAAG
AGACATCTTGGGGTTTAACTGAAATCAATGCATTCAAAAATATGCAGTCAAAGGTTGTTC
CTCTAGACAATATTTTCAGAGTATGCAAATCTCAACCTCCTAGTATATATAACGCGTCAG
CAACCTCTGTTTTTCATAAACACTGTGCCATTCATGTATTTCCATGGACCAGGAATATT
TTGATGTAGAGCCCAGCTTTACTGTGACATATGGAAAGCTAGTTAAGCTACTTTCTCCAA
AGCAACAGCAAAGTAAAACAAAACAAAATGTGTTATCACCTGAAAAAGAGAAGCAGATGT
CAGAGCCACTAGATCAAAAAAAAATTAGGTCAGATCATAATGAAGAAGATGAGAAGGCCT
GTGTGCTACAAGTAGTCTGGAATGGACTTGAAGAATTGAACAATGCCATCAAATATACCA
AAAATGTAGAAGTTCTCCATCTTGGGAAAGTCTGGGTTAGTATAAATTTTATAACTTGGG
AGAAATTTTATGTGGCTTAAACATCCCCAAATTATGAATTAGAATAGTATTTCATATATA
AATTGAAAATCAATTAAAAAGAAACACAGTGCCTAAAGGCACTTGGGGGACACATTTACG
CTTTGCAGTAAAGTCCTTGTTTGGATAAAGATTGTATGTTTTCTGGCCAAGTAAGCTTGA
ATAGGTACAAGCTTAGATAGGTTCAGGCCAGAGAGGTCAAAATTACTTGCCTGAGATTGC
ATAGCTAGTGTTACAACTAGGATTCAAACCCAGGCAGATTGACTTGGGGGTTCATCAGGA
TGGAGTGCCCTACAAAGCCTCCCATCTTTAATGCTTGCAGATTTGTTCCCCAGTTACCGA
AAGCAACTTGTTAATATTAGGGAAAAGGGCCAGTGTAGGGAGAGATCCATGGCATGAGGT
AACCTTCCTGCTGCATGTGGTGGCACCTGGATTGGAATGCATCCAGGAGCTGCTTACCCT
GCCGGTGTCTGCTCTTTAATTTGTGTATAACGGAGAGGAAGTAGACAGGGCAACTAGTGC
TCCAGCCCCTCATCCTGGCCACAAATATTAATGCTACCTTTATATGACATAAGTCACTAG
TCCATTTATTGGAACCTAAATTTGAACCACTGTAAAGTAAGACTTCATAGTGATAAAGAG
AGGAACTTGTTAGGAAAGAGAATAAAATAGAAAGAGAAGGTTGTCTCCTTTTGTAGATTT
TTTTTTTTTCTCCAACAGTTTTACCTGTGACCTTTATACAAATAACTGACAAAGCATTAA
TCTCTTTGGCCTACATCATTTTCTTTTCTATTTTTTTTTTCCACAAGATGGAGTTTCACT
CTTCTTGCCCAAGCTGGAGTGCAGTGGCATGATCTGGCTCACTGCAACCTCCGCCTCCCA

FIGURE 14.4

CGTTCAAGTGGTTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGACTACAGGCATGCACCAC
CACGCCTGGCTAATTTTTTGTATTTTTAGTAGAAACTGGGTTTCACCATGTTAGCCAGCC
TGGTCTGGAACTCCTGACCTCAGGTGATCTGCCTGCCTCGGCCTCCCAAAGTGCTGGGAT
TACAGGCATGAGCCACTGCTCCTGGCCGGCCTACATCATTTTCTAAAGCTCCAGACCATT
CTTTTCTTTTCTTTTCTTTTCTTTTCTTTTCTTTTCTTTTCTTTTCTTTTCTTTTTTCTC
TTCTCTTCTCTTCTCTTCTCTTCTCTTCTCTTCTCTTCTCTTTTCTTTTCTTTTTTTGAG
TTAGAAGCTTGCTTTGTTGCCCAGGCTGGAGTGCAGTGGCACCACCTCCACTCACTACAA
CCTCCACCTCCCAGGTTCAAATGATTCTCCTGCCTCAGCCTTCAGAGTAGCTGGGACTAC
AAGTGTGCGCCACCACTCCTGGCTAATTTTTGTATTTTTAGTAGGGACGAGGTTTCACCA
TGTTGGCCAGGCTAGTCTTGAACTCCTGGTCTCAAGTGATCCGCCTGCCTCAGTCTCCCA
AGGTGCTGGGATTACAGGCGTGAGCCACTGTGCCTGGCCTCAGATCATTATTTTCTGTTA
GCTTTAAACTGTCCGTTCAGGAGATCCCACTGCATCCTCAAATTCAAAATATCTAACACT
GAGCTTATGATTTAGCTGGTTCTGTCATTAGATGGGAATATCCTTTTATTTCCTTGAAAT
TATATGGTGAGAACAGGGAGAAGTGCTGATGGTAAAGTCCTGTGATTAAGATAGCAATAA
GGACTCCGCCCTTCCCACTCCACTGAAGGTTGAAGAGCCATGGACAATGAGAAGTCACAG
TAGGTGAAATCAGGTACTAAAATGGACTTGGCTTGAGAGATCAAAATTGATCACTTGGTG
ATACAACTAACAAATTCATGTTAACTTGAACCTTTATTACCCTGTGAAGCATGGTGATTA
AAAAAAAACAACAAACAAACAGGAAACTTGATTGTTAAATTCTCTTTAAGTCAGAATATG
TACCTTAGAGTTTTTATTTATGCTTTTGTCTACCATTAATATGTCTGCACCTGCTCTTTA
GAAGTTAATAGAGAGTAAAGTCGTCTTTATGTCTTTCAGTGCTTACTTATATTTGGGAAG
TTGAGAAAAATTTTTAACATCATTATTGATATATATATATATATATATATATATATATAT
ATATATATATATATATATATATATAGATAATTTTTTTTTTTTTCTTGAGACGGAGTCTCACT
CTGTCGCCCAGGCCGGAGTGTGGTGGCGATCTCCACTCAATGCAAGCTCTGCCTCCCAGG
TTCAAGCGATTCTCTTGCCTCAGCCTCCCGAGTAGCTAGGATACAGGCTCCCACCACCAC
GCCTGGCTAATTTTTGTAGTTTTAGTAGAGACGAGGTTTCACCATATTGGCCACGCTGGT
CTCAAACTCCTGACCTTGTGATCCGCCCACCTCGGCCTCCCAAAGTGCTGGGATTACAGG
CGTGAGCCACTGCGCCCGGCTGAGGTAAAATTTAAAGTGTACAATTCAGTCATTTTTAGT
ATATTTATACTAGTTGTACAGCCATCACCACAATCTAAGTTTAGAACATTTTCATTAGGG
GGTGGGAGAAATTTTACTCTGCTTTTTAGATTAAGTTTCTGTCTGGATCTAATCATTTAA
TCAGACAATCAGGCAGATTGTCTGTGATTAGTTTTGGCCATTCCAGCTTCTTCATTGGTT
GTTAACTTTCACAAATAAAGGCTGCTCAAAGATTAGAAATAACATTTAATTTGAATGTAA
ATGTGCCATAGTTTAAAAGATGGGTTTGGTGAATACAGTCAAATACATACATTTAAAGCT
CTAATTCTGAAGATTATGTAAAGAAAAGGAAAGAAATGTAGGGAGAGGATTGAAATGTTC
ATGGTATAACAATATCTGAACATCCATCTGGTCACACCGTTGGTATTTGAATGTTTTGTC
CTCCTCAAATTCATATGTCGAAATCCCAACTCCCAAGGTGATCGTATTAGGAGGTGTGGT
CTTTGGGAAGTGATTAGGTCATGAAGGTGAAGCCTTCATGAATGGGATTCGTGCTCTTAT
AAAAGAGAACTGTGAGAAATAAGTTTCTGTCGTTTGTTAGCCACCCAGTTTAGGATATTT
TGATATAGCAGCCTGCATGGACTGAGACAACTATGAGTTATTATGATAGCTTCTGTTATT
TCACCTAAATTCATAGAAGCTAATATATCAATATTTATGCTATGAAATATTTCTTAACCA
AGCTTTGAATATATTTATATTTTTGTTTATTTTTAAATTTCAGATTCCAGATGACCTGAG
GAAGAGACTAAATATAGAAATGCATGCCGTAGTCAGGATAACTCCAGTGGAAGTTACCCC
TAAAATTCCAAGATCTCTAAAGTTACAACCTAGAGAGAATTTAGTGAGTTCAAATATATA
TGTTACATCAAAATTCTTTTACACGTTTTGTAAGATTTCTAGTTGCTTTAGCTAAGTAAT
AAGAATGTTGTATTCCTTTTTGATACAAATCTTTTTTTATTGTGTTAAACTATATATAAC
ATAAAATATGCCATGTTCGCCATTTTTAAGTGTATAATTCAAAGGCATTAATTACATTCA
TAATATTGTACAACCATCACCACTATCTATATCCAGAACTTTTCCATCACCCCAAAGAGA
AACTTGGTACCCATTAAACAATAATTCCCCGTCCACTCCTTTCCCCAGTCCCTGGTAATC
TCTAATGTATATTGTGTCTCTATGAATTTACTTATTCTAGATATTTCATATATAAGTAGA
AGTATGCATTTGTCTTATGTATCTGACTTATTTCATTTAACATAATGTTTTCAAGGCTCA
TCTGTGTTGTATGTATCAGAATGTTATTCCTTTTCATGGCTGAATACTATTCCATTGACT
GCATATACCACATTTGTTTATCCATTCATCTGTTGATGGACACTTGGGTTGTTTCCACAT

FIGURE 14.5

TTTTGGCTGCTGTGAATAATGCTACAGTGAACATTGGTGTACAAGTATCTGTTTGAGTTC
CTCTTTTCAGCTCCTTTGGGATATACCTAGGAATTATGTTTAACTTTTTGAGAAGCTGAG
AAATCTTTAATAAATGATAACACAAATACTTATATTTGCCAATGCAAATATGAATATTTT
TGGCTTTTAAGAGATTGATCATTTTGCCACGTGGTTGTAATTAAAAAAAATTGTCCCATG
TTGTTTCAGTATTAATATTGTAGCCTAAAAGAGTGCTAGACTGTTTTACTTTTTACTCAG
TTAATTCTTTGGATACTGGTAGAGTCAGGAAATGAGATATTGAACTTAAAGATCTTTGCA
GGTGGGGTCCAGTGGCTCACACCTGTAATCCTAGCACTTTGGGAAGCTGAGGTGGGAGGA
TTGCTTGAGGCCAAGAGTTTGAGAATAGCCTGGGCAACATAGCAAGACCCCATCTCTACA
AAAAAATTAAAAAAAAAATTAAGCCAGGCGTGGTAGCTCACGCCTGTTATCCCAACACTT
CGGGAGGCTGAGATGGGTGGATCACTTGAGGTCAGGAGTTGGAGACCAGCCTGGCCAACA
TGGTGAAACCCCATCTCTACTAAAAATACCAAAATTATCGGGGCGTGGTGCTAATCCTGT
AATCTCAGCTACTCAGGAGGCTGAGGCAGGAGAACCACTTGAACTGAGGAGGTGGAAGTT
GCAGTGAGCCTAGATCTCACCACTGCACTCCAGCCTGGGTAACAGAGCGAGACTCTATTT
CAAAAAAAGTAAAAATAAAAATTAGACACATGTGGTGGCACATGCCTGTAGTCCTAGCTA
CTCAGGAGGCTGACTGAAGTGGGAGGATCTCTTGAGCCCAGGAGTTCCACACTGCAGTGA
GCTATGATTGTGCCACTGCACTCCAGCCTAGGCAATATCTCAAAAAAAATTTTTTTAAAT
AGATTATTAGGCCAGACGTGGTGGCTCATGCCAGTAATCCCAGCACTTTGGAAGGCCAAG
GCAGGCGGATCACCTGAGGCCAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCC
ATGTCTACCAAAAATACAAAAATTAGCTGCAATGTCTATAATCCCAGCTACTTGGGAGCC
TGAGGCAAGCGAATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGTGGAGACTGCGCC
ACTGCACTCCAGCCTGGGCGATACAGCGAGATTCTGTCTCAAAGAAAAAGGAATTTGTTT
TCCTGTCTTTATCGTAGAGGGAGGAAAGGGAGAATGGGGTTGGAATGGTTATTGAGTGAG
CCACATTATGGTAGATGTATCACTGGGCATAGAGAAAAGGAGCATTTAAAACTTTTCCGC
CTAACAGATGTTTCTTCAGGCTACACTGCACTCATTGTGCTAACTGTAATGTCAAATCCC
AGACCTGTGCCTATAGAACATGAACATCCTTCATTGGATTTGTTTGGTCAGGCTTACACT
TTATTAGGAAGATCAGATGTTAAAATAAGGGTGTTAAAGTTAAGTTCAGATATGAGGATA
ATTCATTACTATTCCTTTTTCTGGCAGCCTAAAGACATAAGTGAAGAAGACATAAAAACT
GTATTTTATTCATGGCTACAGCAGTCTACTACCACCATGCTTCCTTTGGTAATATCAGAG
GAAGAATTTATTAAGCTGGAAACTAAAGATGGTGAGTACATTTGTTATTTTGACTTTTTT
TTCTATTTAAATAGTTGTACATTTTTAATTGTTCTTGCAACCTGTCATACCTGTGAACAG
TATGTGAATAGTGAAATATAATTATGATAATTAAACAGTAGTTTTTATGTATTGAAAAAT
ATCTTTGGCCGGGTGCAGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCA
GGCGGATCACTTGAGGCCAGGAGTTCGAGAGCAGCCTGCCAACATGGCGCAACCCTATCT
ATACAAAAAAATACAAAAATTAGCCTGACATAGTGGTGTATGCCTGTAGTCCCAGCTACT
TGGGAGGCTGAGGCAGAAGGATCACTTGAGCCCAGGAGGTCTGTGTTCCTGCCACTGCAC
TCCAGCCTGGGCAGCAGAGTGAGACCCTGTTGGGGGGAAAAAAAAAAAAGTCTTTAACTT
AAATAAATTTGACATTTAAAATCTTAAATTATTTCATCTCTGTTTCAGTACTAACTCTGC
ATTTATTACTTTCTTTTTAATAGGACTGAAGGAATTTTCTCTGAGTATAGTTCATTCTTG
GGAAAAAGAAAAAGATAAAAATATTTTTCTGTTGAGTCCCAATTTGCTGCAGAAGACTAC
AATACAAGTAATAGCATGTTATTGAATATTTAATAAAATACTATTTGTTACATATGATTG
ATAATAAAGTATGAAGTTCCTTGTAACACCTTGCATTGTGAAGTGTATTAAAAACCTGCT
AAGAGTAAGGAATAACTTGATTTAAAATATTTTATTCTGTAATCTCTTTAAATTATCTGT
ACAAATTATTGACTTAACCTAAATTTAAAAATGAATGCCTTAGCACAATTAAGTTCCAAG
AATAGAGTTGATCATGTTAACTGGTAAATGGATCATGATTTAAAATTCTTCTAGGATTGA
AACAAATGAAAACGTAGTTTTAAGGGTTTGATTTTTTAAATTCCTATTTTTACATGCAAT
TTTACTGCACAACCCATCTTATTTTGACAGTTCTTAAATTCGCAACTCTTCAGAAATATT
ATCAGATCACTTTTCTTTGCTTCCATAAGTTTTTTTATTATTATATTATTATTTTTTTTT
TTTAAAAGACGGTGTCTCACTTTGTCGCCCAGGCTGGAGTGCAGTGGCATGATCATGGCT
CACTGCAGCCTCGACCTCCCAGGCTCAGGTGATTCTCCCACCTCAGCCTCCCAAGTAGCT
GGGACCACAGGCGAATGCCATGATGCCTGGCTAATTTTTGTATGTTTTGTAGAGATAGGG
TTTCACCATGTTGCCCAGAATTGTCTTGAACTCCTGGGTTCAAGCAGTTGTTCTGCCTTG
CCCACCCAAAGTTGTGGGATTACAAGTGTGAGCCACTGCGCCCAGCTATTCTAGAAGTAT

FIGURE 14.6

TTTAAGAGTCATCTTTTTTTTTTTTTTGAGATGGAGTCTCACTCTGTCACCCAGGCTGGA
GTGCAGTGGCACACTCTCGGCTCACTGCAACCTCCACCTCCTGGGTTCAAGTGATTCTCC
TGCCTCAGCTTCCCTAGTAGCTAGGATTACAGGCGCATGCCACCATGCCCTGCTATTTTT
TGTAGTTTTAGTAGAGACGAGATTTCACCATGTTGGCCAGGCTGCTCTTGAACTCCTGAC
CTCAAGTGATCTGCCCTCCTCAGCCTCCCAAAGTGCTGGGATTCTAAGTGTAAACCACCA
CACCCAGCCAAGAGTGGTCTTTTTACAATATTATTTTTTGATTAGGACATTCATTCTTGT
CATAAAATTGAAGATACTCTAGTCATTTAGAATTTCATTGTTTTGGAACTAGACATTGTT
TCTTTATTTTTGAAATGTTATTGAAGGAATACCATTTGGAGAAGATACAAATGTAAGAAT
TGTGAAAAGGATAATTGTGACACAAATCAAAATTATAGATAAAAATATACCTGTAAAATG
TATTAAGGCAATAACATTCTTTCTGCTTGTTGACCATAAATATTTATATTCCCTGGATGG
GTACATTGTTATTGTCAAGGGTGTTTAAATAATGATCTTGCATGCATAATTTATTCTCTC
TGGTATAACAGAATCAGCAATTTAGTTTTCTGGGACCCGAGAAAAACATGCAAAAGACAT
ACTTTGAAATGTAAAACTGATTTTTCCTTGCAACTGTAGGTCCTTCTAGATCCTATGGTA
AAAGAAGAAAACAGTGAGGAAATTGACTTTATTCTTCCTTTTTTAAAGCTGAGCTCTTTG
GGGTAAGAAGTTATGGCCAAACTAGCATGTTAGACATGTTTTTAACACTATATCTGGCAG
AGTTTTCAATGTAAATATTAAAGTAGATGTTAATGTCAATAAGTGATCTTAATAATGCAT
CAGTAGATATTTTTTTCAAGGATTGTCTCTATCTTCACGCCTAGCTTATAATTTGCCTTGT
CGTCTTTTTTTTTTTCTCTTTATTTTTATGTTTTTATCCATCCCTGGTGGTAGGGGATAA
CCTTGTCTTCTTCGATAACAAGAAGTCTGAAGCTTATTAGAAATTTTACTTTGAGAATTG
ATCGATGAGAAGAAAGCAACTAGATATCACGTGGATCATATATGCTTGAATAAAACAATA
ATTCTTAGAACAAATAAATACATTTTAAAAGTTAAAGCCAAAAACATTAGTTGAATGTTT
AAAAATATTTCAAATTAAGTTATTCCTTCACTGTCTTGTATTACTGTAATAATTTGGATT
ATTTGTGTTTTTCTCAACTTTTAAAACAAATATTTAAAAAATTCCTCTTTTGATTAAGTA
GGGCTAGATAAAATATAAAAAATATTTTTTAAACTCCTCTTAATTTCCATATTTCTTATA
TAATATGAGAATCTCTTATAAACACTACCTCTTAGAAGTCTCCACAGAAGCTTTGGTAGA
TGTAGTAGTAGGGATTTGATTTCTTAGAATGGTATAATCTGTAAATGTTTTAGTAAAAGG
ATTAAACGATAAAGTCAAAATGTTTATAGCACAGTGTTTATTAATATAAAATAAAATCTC
TTTTTTTTTTTTTGAGATGGACTCTCACTTTGTCACTCAGGCTGGAGTGCAGTGTTGCAA
TCTCAGCTCATTGCAACCTCCGCCTCCTGGGTTCAAGCAATCCTTCCGCATCAGCCTCCT
AAGTAGCTGGGATTACAAGCATGCACCACCACACCTGCCTAATTTTTTGTATTTTTAGTA
GAGATGGGGTTTCACCATGTTGGCCAGGCTGGTCTCAAGTGATCCGCCTGCCTCAGCCTC
CCAAAGTGCTGGGATTACAGGCGTGAACCACTGTGCCCAGCATAAAGTAAAATCTCTTCA
GACTCTCATGTGATCATGTAAAGTGGCAGGCAGTCACAGTCAAGAAGTAGTTTAAAGTTC
ATGTTTGTAAAATATAATCTACAGATTGATACTGGATTTCATAGGTAATGTTTAAGAGAA
AATAAGTTTTTAGTTATCCTCAGTACTTCAAAAGCACCCATTTATGATTATGTTGATTAC
TAAACTAAATCATTTGGGGGCTAGAGGTGTTTTTTTATGTGTTAAGATTCCTTAAGGAGT
TCTATTAGGGCAAAACTTTTAGTAACTGCATATTTTAAAAGTAATAAAACTAATTTTAAA
AGCTTGGAGGCTGGGCGCGGTGGCTCACACCTGTAATTCCAGCACTTTGGGAGGCCAAGG
CGGGTGGATCACTTGAGGTCAGGAGTTTGAGACGAGCCTGAGCAACATGGTGAAACCTTG
TCTCTACTAAAAATACAGAAATTAGCCAGGTGTGGTGGTGGGCACCTGTAATCCCAGCTA
CTCGGGAGGCTAAGGCAGGAGAATTGCTCGAACTTGGGAGGCAGAGGTTGCAGTGAGCCG
AGATCATGCCACTGCACTCCAGCCTGGGTGACAGAGCAAGACTCCGTCTCAAAAAAAAAA
AAAAAAAAAAGCTTGAAGTCAGATTCGACATTAATCAGTATACTTTCTCTCAAGTAGGGG
ACAATTTCTAAGATTTTAGTCTTTTAAAATTTATTAACTAGTCTGAGCATGGTGGCTTGT
GTCTATAATCCCAGCACTTTGTGGGGCCGAGGCAGATGGATCACTTGAGCCCAGGAGTTG
GAGACTAGCCTGGGCAACATGGCAAAACCCCGTCTCTACAACAAATGCACACACAAAAAA
CCCAATCAGCTGGGTGTGGTGTTACACTCCTGAAGTCCCAGCTACTCGGGAGGCTGAGGC
AGGAGGATCACCTTTGCCAGGGCGTTTGAGGCTGCAGGGAGCTGGGTTCACACCACTGCG
CTCCAGCCTGGATGACACAGCAAGCCCCTTTCTCAAAAAAAAAAAAGATAAAAAATTAAAT
TAAATTAATTAACTACACTGGGAAGGCAAAATTCAGCATTTTTTTATAGCTAAATTTTAT
CCTGCTTCAGTCTTTTATCATGTAACTATGTATATTTTTTACAGAGGAGTGAATTCCTTA
GGCGTATCCTCCTTGGAGCACATCACTCACAGCCTCCTGGGACGCCCTTTGTCTCGGCAG

FIGURE 14.7

CTGATGTCTCTTGTTGCAGGACTTAGGAATGGAGCTCTTTTACTCACAGGAGGAAAGGTA
AGTGGTTAAGGTGTGTTCATTTTTCTGTAACATTTAATAACTTTTCATTTATCTTTCTTT
GGGTTTTGACCATCTATTATATAGGGTGGGTTTTGACCATCTATTATATAGGGTTTATAC
GACATATGGAAAGCATTCATTTATTCACTAATATTTCTGTGTGTCTGCTTTTAGGTGTTG
GGGGAGTGATGACGAATAAGACTGATGTTCTCCATGCCCTTTTTCTGTGTCAGTTGATAC
AATTATATGGTTTTTCTTTTTTAGGCTATTAGGTGTTGATAGGGTTGAGTAACTTACAAA
TGTTGAACCAGCCTTGCATACCTGTGATAAATACCACGTAGTTGTGGTGTATCATTCTTT
CTACATTGCTGAGTTTTATCTGCTAATGTTCTGTTGAGCTTTTGTCCATTTAAGTTTGAA
AGTGATTAGTTTGCAGTTTTCTGTTTTTGTGTTGTCTTTGTCTGGTTTTGCTATCCGTGT
AAATCTGGCCTCATAAAATGAGATGGGAAGTATTCTCTCCTCTTCTTTTGTTTTTTTGGA
AGAGGTTGTATAAAATTGAGGCTGAATCTTGGTGGTTGCCACAATGACAGGAACTATTTC
TGTGACTGAATATATTGGGAATTCCTATAAAGCAATTATTTTCTAGGGAAGTGGAAAATC
AACTTTAGCCAAAGCAATCTGTAAAGAAGCATTTGACAAACTGGATGCCCATGTGGAGAG
AGTTGACTGTAAAGCTTTACGAGGTATGAGTATGGTAACACTCTATATAAATCCCTTTTT
CATTAGAAAGACAGGAATGTTATACATAATGCTGTCAATCTAATAAATACACATATCATC
TAGTCTTTAACTTTTCTGTTTATCATTTAGTCATTAAAATTTCTTTGGCTTTCTAATGTT
TTTGATAAAATTTCTAAAACTCTCCATATTTAATGGAGGCCTATTTTTTTTTCTAGCCAG
AACTTTTTGTAGACTACATTTCTGGAAGTGCTCACTGACACCACTCTGAAAAATTAGTAC
TTAGAATATACTCTAATTGGTATAAATGATCTCTGAATTGCTATGGAAAACTGGGAGAAT
GGTTGCTTCAGGGGAGAGAAAGTAGGAGGCTGTGGACAGCAATGAGGAGAATTACAGTTC
ACCATATAACACTTTTGTACTTTTAAAGTCCTTAACATTTACATTATTATCTATTCAATT
AAAAAATATTGGGAAGATTTTACTTTGAACAGTTAATTTTTCCCCCATGGGTACCGCTGT
CATATAGTTCCAACTAATCATGAACTTGTGTATTTCCTGTTCTTTGTAAATTTAAACTTT
GTAACTCACCAGGAAGTTTGAAGCCAAATTTGTGTTTCAAATATAGCAACTCCAGGATCT
CTAGGCAGATGCATTTGCATTTGATTTTAAATGAATCTTGATCCCTTACTCTCACTTATG
TTTTCCCACATCCTACTTTTTTTATTTTGTTGTAAGCCATCTAAAATTCTCAATGGGATG
AAACTGGGTATAAATGAATACATGCATACAGGAATTATAGTAGCATATTCCTTTTCTTTT
TTCTTTTTTTTTTTTTTGAGACAGAGTCTTGCTCTGTAGCCCAGGCTGGAGTGCAGTGG
TGCGATCTCGGCTCACTATAGCCTCCACCTCCCAGGTTCAAGCAATTCTCGTGCCTCAAC
CTCCCGAGTAATTGGGACTACAGGTGCATGCCACCACACCTGGCTAATTTTTGTATTTTT
TAGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTGATCTCAAACTCCTGACCTCAAAGT
GATCTGCCTGCCTTGGTTTCCCAAAGTGCTGGGATTACTAGCATAAGCCACTGCACCTGG
CCTCCTTTTCTGAGTTTTATAAAATTTGATACTTTACTGCACGCTTTGAGACTGTATTAA
TTGAACCATGTTGATGAACAAGTTTTTGTGATGGGTATATTAATAAAATATAGATCAAAT
TTTTATAGTTAAATCAATATCGAGCTTTTCTAGTGCTTTCAAAAGGACAACCTGAATTTT
CCCAGCACTGAAATGATACTGAAACCATTTCATATCTTCTGTATTAAGGAAAAAGGCTTG
AAAACATACAAAAAACCCTAGAGGTGGCTTTCTCAGAGGCAGTGTGGATGCAGCCATCTG
TTGTCCTGCTGGATGACCTTGACCTCATTGCTGGACTGCCTGCTGTCCCGGAACATGAGC
ACAGTCCTGATGCGGTGCAGAGCCAGCGGCTTGCTCATGGTAAATGCATCCACCACTGGC
TTAAGGTCTTGTTCTTTTGTCAGTCAGCATTTTTAGTCTTAACAATAAATCTACTCTCTT
CAGAGAATAATATATGTGTTATGTTAAGTGTTGTGTTTGAGGCCCCTGATGGCATTCTAC
AGTTGTCCTATAGACTGTAATAGCAAAATTGGTAGAGTAAAAACAGTGTGAAAATTCTGC
AACTTCATGGTTAGTCCTTTAGGGTTTTTCATTCTCCCTTACTTATTGTTTAATTTACAG
ATTTACTCTTTTGTTCATTTGACAAATATTTGTCAAATGCTTGTGCACAGTCTGTATTCT
CAAATTCTAGGAGAAAAAGAAGGGTGAACAGTATTAGCGCAGAACGATACTAATAATGAT
GGCTACTGTGTATGAGTAGCCAGCCCTTTCTTGGCTTTCTTGGATTGCTTTGTATTCTAC
ATGAAGATATTCCCTGGGCTTTACAGGTCAATAAATGGAAATTCAGAGAGATTAATTTGA
CCAGGGTGACCAACAAGGAGATGACAGCATACACTATGCGAGAAGTATACACAGAGTAGT
GTAGGAGCATATAACCTAAACTGGGGGTGAGGTGGGATAAGGAGTTATCAGGGAAGGCTT
TTTGGAGGAGTTGACAACTGAGCCGAGTTTTGATGGAAGAGTAGAAATTAGCATGAACCA
ATTTCATGCTAATAAAGAAGCAAAGGAAGCGTGGTCTACAGGCAAAAGCACAGAGGTACA
GGAAGTAATGATATGTTGGGGAATACCCTGTTGACTGGAGCTTAGAGTGCAAGGAGAGGA

FIGURE 14.8

GTGCTAGGGAGGTGAGGTTGGAGGGTTTGGCAGCATTGACTTGCTTCAAGGTTCTTAAGA
GCTGAAATAGATATAAAATGCAACTAAGAGTGGCTTGGATTATTATTACCTAGTGTGTTA
ATCTCAAATTTTGAAATCTATAGCATCTATAGGACTGGTGTTACTAATCTTACACTCGAT
CTGTTACTGTTCTTATACTAGATCTATTAGTCCAGTGTTTAAGGGAGTGGTGCAGATTTC
TAGGTCAGGACAGGACTCAGATGTACATTATTAATGCCTATTTCAGTTCTGACCTTCTCA
TATGAAACCTTATAAGACCTGGGGTAGGAAGAGATTGTTCTGGAAGTCATAGGAATATGA
ACTGTATTTTGTTTAACAAACAATACAGTATGGAAATTTATCACCCTTCCAGAATATTTA
TTTCAGAGACAAATTTTTATCATTCGTTCATTTATTTCATAAGATCCACGAGTAGGGAAC
CTCACTAGACATTGCTCTGAGTATATGGTCTGAGTTTGCAGTACCTCTTGTGTCTCCATT
AGATTTATTAGGTCCTCAATAGATAAATCAGGGAATAACTAGATGGATTCATTTTTTAAA
GACATGAAAGAGCGATACCATACATACTGCACCTTAAAGGTCAACCTTAGAGTATCATTA
TTTTTAATGAATGTATAATTTTTAAATTTCATGTTTACTTTTCCTAAGCTTTTGCACTAT
ATTGCTTAATTCCAGCTTTGAATGATATGATAAAAGAGTTTATCTCCATGGGAAGTTTGG
TTGCACTGATTGCCACAAGTCAGTCTCAGCAATCTCTACATCCTTTACTTGTTTCTGCTC
AAGGAGTTCACATATTTCAGTGCGTCCAACACATTCAGCCTCCTAATCAGGTAATACACT
ACTTGTAAGGATTATTGAATTATGTCCCTTTTATAGAAATTATTTTTCAATTTTATTAGT
AATTCGTGGCTTTAAATTTATGCTTCTCTTAATGATTTTAAGGATATGTAAGTCAACATT
TGGTGCATATTGTGCTAGAGGCATAAATTATAATTTATAGCCACCTGAAATGTTAGTATG
CGCTTTCCAAGAAAATGACTTTTTTGAAAATGGTATTTCTTTGAATGAGAAAGAACAGAG
AGAAATAGATAGATGGCTTTTAAACACTTCATTAATTAAACTTTTTTTTCCACCATCAC
ATAATGGCACTTAGTCCCCTTTGGGAACTCATGAGGGTTTTAGTGGTAGTGAGCTGAAAG
AAATATGTTCCAGGACTGGCAAACATATTCTAAATTCTTTAAAATTTTCACCTAGCATCT
ACCCTAAATATTCAGACCCTGTGCTAGTTAACTGCTATTGAAGAACAAAGGTATTATATC
TATTATTAAGGATAATAGAATGGTATTTGAGATATTGGTCATTGAATATGAATATGTTTT
GAGAAATAAGTTTTATAGGAACCAAAAAAAAATTCTTAAAGGAACCATATATTACTAAAA
ATGCTTCTTATTGGAGAAAGAAATGACAATCATTTATTAATGTGATTTTTTCACAACTTT
ATTAAGATATAATTTAAGTACAACAAACTCACATAAAGTGTACAATTTGATCAGTTTTAA
CATATGTAGATGCCATGAAACCATCACCACAATTAAGGAAACAAACATTTTCATCACTCC
AGAAGTCTCCTAGCCCTTTTACTACCCATTCCTCCCCTGCTCCATCCCCAGACAACTACC
AATTTGCTTTCTGTCACTATAGATTTGTCAACCTGATTTTCTCCAAATATACATTCAAAA
ATATACAGTTGAATACAATTGGAAATTCGAATTTTGTGTTTTTTTCTTTAGGAACAAAGA
TGTGAAATTCTGTGTAATGTAATAAAAAATAAATTGGACTGTGATATAAACAAGTTCACC
GATCTTGACCTGCAGCATGTAGCTAAAGAAACTGGCGGGTTTGTGGCTAGAGATTTTACA
GTACTTGTGGATCGAGCCATACATTCTCGACTCTCTCGTCAGAGTATATCCACCAGAGAA
AGTATGTTTTACTATTAAAACCTGAACTTGGAATCTTCTTTCTATTGTGGAGAAATGTAA
TTGTAGTAAGACAAGAATTAAATATATTCCATTGTAGTATTTGAATAAGCAGTTATTTGA
GTAGAAAATTAGTGTTTCCAGCTAAGATGATGGCATATTTTGAAAATTCATATAGTGAAT
ATAACTAGTAAAAGAAGTTTTGTTTATTTTTAAACAGAATTAGTTTTAACAACATTGGAC
TTCCAAAAGGCTCTCCGCGGATTTCTTCCTGCGTCTTTGCGAAGTGTCAACCTGCATAAA
CCTAGAGACCTGGGTTGGGACAAGATTGGTGGGTTACATGAAGTTAGGCAGATACTCATG
GATACTATCCAGTTACCTGCCAAGGTATGTTTAAAAAAAGAAAAAGTGAATACTTACTCC
CAGAAGAACCACTGTATTATTGGCTTTGGCTTTATGTGTCAGCTTGCCCAATCTCCGTGT
GAGTCAACAAGTGTTTACTGAGTTACCAAATAAATGTCTTAACACTATTTTAGGTACTTT
AACAAATTTTAATTTTATTAATTAATTTTTTATTAGAATTGAGACCTCACTCTGTCATCT
AGGCTGGAGTACACTCACAGCTCACTGCAACCTCAAACTCCTGGGCTCAAGCAATCCTCC
TGCCTCAGCCTCCCCAGTAGCTAGAACTACAGGCATGAACCACCATGCCCGGCCAACTCT
TTAATTTTCTTAGAGACGGAGTCTTGCTATGTTGCCCAGGCAGACAGATTTTAATGTGTA
TGATGCAGTCTTTGATGATAAGAAACTTATAATGGAAAGCTGAGGTGATAGTTACAGTAA
ATACATTTTGATGTATAATTCTGTTTGCTTTAATCATTCAAATTGTAGTAAAGCAAGATG
AACTGTCTGCTGGGATTTGAGCAGAAATGGATAGGAATAAACTAGGAGGTAGAAGAGTTA
TCAAGGTTCACAGGACTGATGGGTGAAGCTAGATTTCCAGACCCGGGATGTCAGTCCTTG
AAAAGCAGACTTGGCAGGCATAGACGAGGCAGATAGCAGGATAAAGGAGACAAATGTAGA

FIGURE 14.9

TTGTTCTTCAGAAGATCAGATGGTAGAGTCTAGGAGGTAGTGTGTTTTAATCAGAGATCT
GAGAGGCAAAGATCATTGCATGAGATCAGGGACCCATGCAAAGGAGTGAGAAAAAAAACT
GGGTTAAGGAGCCTGCTGCATGGCAACTCCTGGGAACAGTGGCCACTGGGGCCTGGGACA
TGTTGATTGCAGCCCAGGACTGTTAAAACCAGTGTGAGAGAACATGGGTATGGAAGTACT
AGCTAGCAGGATCATGACCCCGATGCTGGGATGGGGCATCAAGCATTAGTACATGGAGAT
TCAGTACATCCAGATGCAGTACATGGAGACTATATGCGTAACTGCTGACTTTGGGCTTCT
TTCAGATTGGAGCAGAGGTAGAGGTGAGTGGGAATATTCTCAATAGAGGGAACTAAATAG
GCATACCTAATAAAGGAGACCAGGATATTGCAGACAGTAGCCTCATGTTTGGCTCACCTG
TTCAAAAAGTTCTCTTGTTCTTGAGCAGTGGTGCCTTAAAAGGTAACTTGAGAAGCAGTC
GATTATTTGTTCAGCCTGGAGACTCTTGGGATATTTTACTATCTTTGATTGAATAGATTT
AAATGTACACAGCTCTCATAACTTGCCCCATGAAGCATATCCATGAAAGGCACTATACTT
GTTAAAAGATTGGTTTGTACTTTTTAAATGTAGTACTTTTAATAAAACAGGAAAAATAGA
AGTTCTGATGCAGTTATATGCATTTTATATAGAATGTGTTCTTAATTGGAAAAAATTTGT
CGTAGTTCCTTTGAGTTCATTTACAGTTTTTAGTAGGAATTGTATTTTCTACTGTTGTAC
TTGCTGTTACTAAAGAAAGATGGTCGTGATTACCATCTGAATTTTTTTTCTATACATTGA
TCTTTAGCTGCTACTTAGTCATTTCTGTTTAGACTTGAGCTCTTTTTCATATTTTTTTTT
TTTGTTTCTCAGTATCCAGAATTATTTGCAAACTTGCCCATACGACAAAGAACAGGAATA
CTGTTGTATGGTCCGCCTGGAACAGGAAAAACCTTACTAGCTGGGGTAATTGCACGAGAG
AGTAGAATGAATTTTATAAGTGTCAAGGTATGTTGTCTACTTATCTTCTTTTTTTATTTA
GGTAAAATTAACATAAATGCAGTTAGCCATTTCAAAGTGTAAATTCACTGGCATTTAGTG
CATTCACAATGCTATGCAACCACCACCTCTCTCTAATTTCAAAACTTTTTCATTCCACTC
CTCCTCTTGCTTATCCCCTGGCAACCATTCATCTGCTTTTTGTCTCTATGGATTTGCCTT
TTCTGTATATTTCATATAAAACAAATCATGCAATATGTGACCTTTTTTGTCTGGCTTCTT
TCACTTATGTAATGTTTTCATGGTTCATCCAGGTAGTAGCATGTATCAGTACTTCATTCC
TTTGCATGACTGAATAATGTTACCATACTTTGTTTATCCACTTATCAGTGGTGAACATTT
GAATTGTTTCTACCTTTTGACTATTATGAATAATGTTGCTGTAAATATTCATGCACAAAT
TTCTCCACGGATATGTTTTCATTTCTCTTGGGTATAAACTGAGGAGTAGAATTCTTGGGT
CTTAGGGTAATTCTCTAACTTTTCAAAGAACCACCAAACTGTCTTTCACACCAACTGCAC
CATTCCCACTAGCAGTGTGGGGGGTTCCTGATTCTCCACATCTTTACCAACACCATTATG
TTTCTCAATTGTGGGCTAGTCTCACATTTGGAAAGCTAGTGGGAGCAGCGATCCATCTAT
TAAAAGTTGTATGAAATTGAGTAATGAGCCACCTCTCTCTTGTAGGGCTTATTATGTTCT
TGCTTAAGGCAATCTTCATGCATTGTGAACAGAATTATACATAAATGCTCAGATAAAAGG
GCAAACCATTCTTAAAGGGAGTAGACAACTAGAGGCAGGAGACCATACTGAGGCAGGAAG
CTGGGGTTTTTATGGTTCTGTTACTTTTGACTATATCTCACCATTGCTTTTGTCAAAGTG
AGACTAGGTCTAAGTTTTTTTCAGGTATAAGGTGAGTGTGGTAATTAAGGGGCATGCTAG
CAGATCATTTTGGGTAATGCTTCACAGTCCACCACTGGTGTGTCATTGTGGTCGCAGATC
CAGTATCTTAGCTGTGTAATTTCAGACATCAGCAATATTAGTTTAACAAAGGGCAATTAG
ATTCCAAGACAAAGGAATCGTGTATTATTCTAGCCTTATTCAAACTTGATTTATAAATCA
GTTTAGTAATTTATTTATTTGTTTCTGTATTTATTTTTATTTCTTTGAGATGGAGTCTCA
CTCTATTGGCCAGGCTGGAGTGTAGTGATGCAATCTTGGCTTACTGCAACCTCTGCCTCC
TGGGTTCAAGCTATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCTAATTTT
TGTATTTTTAGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTGGTCTTGAACTCCTGAC
CTCGAGTGATCTGCCCGCCTTGGCCTCCCAAAGTTCTGGGATTACAGACGTGAGCTACCG
TGCCCAGCTCAGTTTAGTAATGTATAACTGGGTTTTACCCAGTTGTAAATTACTCTTTTG
TCGTGTTTTTTTGAGAACTGGCAATGACGGAGAAACTAAAAGTGCCAGGCTGTTGCCTTG
TTCCTGTTATTTTGCCTTAGTTTTTTTTTTTTTTTTTTTTCTCTGAGACTGAGTCTTG
TTGTGTTACCAGGCTAGAGTGGAGTGGCATGATCTCGGCTCACTGCAACCTCTGCCTCCT
GGGTTCAAGTGATTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGCCTGCCACC
GCACCCGGTGAATTTTTGTATTTTTAGTAGAGACGGGATTTTACCATGTTGGCCAGGCTG
GCCTCGACCTCCTGACCTCATGATCCACCAGCTTCGGCCTCCCAAAGTGCTGGGATTACA
GGCGAGAACCACCGTGCCCGGTCTTGCCTTAGTTATTTCTTGTTCCCTCCTCTAGTCCTA
TAGTTCTCTGACTGTATTGAGGAAATGTAATTAAATATTATTATGTTAATAGATATTTAT

FIGURE 14.10

GTGGTTGAATATTAGAAATTCCTTATTTTGGTCACATATCCTGATCAGTAGTTGGTCTTC
TGGAGATAGTGATTTTTCACTAGAGATGACTTTAGGACCTATTCAGGTTTTTTTTAAGAT
CCCAATTTAAGGAAAGACTATTCTCATTATTGATTTTGCTATATGCAGGGAAATTTATTT
CGAAAGGTTTTTCAGTTGGCTTTTAGGGAAGATTATATATTCTCTTTTTTTTTTTTTGGC
CTTTTCCCACATGTTCTAAAAATGATATATTCTTTAACTCCTATGAAAATACATTGTTTC
AGTAATTGAAGATGCTGATTAAAGTCATATCTCTACACATTTTTTAAAATTTGAGATAGA
TGGGACTTTGTCCCTTCTTACACCATTCACTTATTCACTTGGAAAAACTATTATCCAATA
CTTATGTGGCAGACACTGTTTCTGGCACAAGGGATTCAGCAGTGAACAAAACTGCCTTTT
TGGAGTTTACATTCTACTAGTGGAAAGCGACAACAAGCAGATAGACACATTCAGTATATA
ATTCACTGTCAGATGGTGGTGGTAAGTCCTATGTAGGAAGAAAAGCAGGGTAAGGAGGCT
TGGAGTAACTGGAGTGAGTCATAGATGGACTTGTCAGGAAAGGGTTTCTGAAGAGGTGGT
ATTTGGGCAGAGATCTAAATAAAATGAAGCAACAAGCCATGAGAATATCCGGGGGAAAAT
GTTCTGGGCAGAAGCATCAAGCATAGAACTTGTGGTATGATATTTATTCTAGCACACATT
AATTTTAAAAATGTATAAAAGACATCCATTTAATCATATTAAAGATTTCCATGATTCATT
TAGACTTAGTCAGAAACCAAATTTATATTTTCTTTTTAAATAATTTTATCTCAACTCTTA
TTTTACCCAATAGGGGCCAGAGTTACTCAGCAAATACATTGGAGCAAGTGAACAAGCTGT
TCGGGATATTTTTATTAGGTTGGTAGCCTATGAATGTTTTTAAAGTAACTGACTCTGTTA
TTATTTATCAATCAGTGCTTTTTTTGGTCTTGTTTTTTGAAGAACTGATATTTGAAACCT
GTGGTTTATGTGAATTATTAATAAGCTAGAGGACGTGGATTCTCTATTTCATCAAATAAT
ACAAAACATTTTAGATATTAAATTTTGGAAATTATTTGGTTTTGTTTTACAATAGAAATA
CTCCTCAAAGTGGAATCGAAGTGGTTATTCAAAGAAATCTCAGAGTAGATTCTTATATGA
AGCAAATAATTGCCCCTAATTTATCTCTAAATTTTGTAAGTTCTAAATTCTTTTTTCCCC
CAGTTTCTAATTTATCTCTTATAAGTCAAGAGTCCATCTGGCCAATTTAATTTCAGTGAG
TGTAACTATTTTGCATATATTAAAAAACTGTATATGAATACAGAAGATGGTATTTAAGGA
TGAAAATAATTATTCAAATGTGATAGCATTATGGGGAGTTTTAAAATAAAAGTTACTGTT
TTATTCTTCCAAAAATTTTATTATAAAGTATACAGTTAAGAGAATATACATAAAATACAT
ATGCAGCTTAAGGAAGAATAATAAAATGAATACTTCATGTATTCACCACCGAGTTTACCA
GGAAAAAGCATAAACAAAATAAACCTCTTCCACGTAATTCCTGGGTTAAAGAGAAGTTAT
AGTGGAAAATATTTGGGAGCAAACGATAATGAAAATACTATCCATTAAAATTGTTAGATG
TTGCAAAACTGATTTCAAGGAAAATTTATAGTGTTAAATGTTTAGAAAAGAAAAAAGGTT
AGAAGTTAACCACTTATGTATCTATCTCATGAAATTAGGAAAATTATAGATATAAACTAA
AAAATATGTTAAAAGGGAAATAATAAAGATAAGAATGAAGTTTAATGAAACACAAAACAG
AGAAGCTCACAAAGCCAAGATTTATTTTTTGAACACCGAGTACAATTGACAAATCTCTAA
CAAGTTTGATTAAGAAAAAAGAAAGCATGAATAAACAATTTTAGGGATAAAAAGGGAAAC
ATCGCTAAAGATATCCCAGAAATGTAAAAGATAATAAGGGAATATTATGAAAATATTCAT
GCCAATACATTTGAAAACTTAGGTGACATAGACAAAAACAAAATTGACCAAAATTGAGCA
AAAAAGAAACAAAATCTGAGTAGTCCTGTAACTTAGTAAAAATTGAGTTAGAAAAGTTAA
AGAAGTCTTTACACAAATCAAACATCAGACTCAGTTTTCTAGGAGAGTTTTGCCAAACAT
TCAAGTAGCAGATAATTCTGGTCTATTTTTGGCCCCAGAAGATATATTTTACTTGCCATG
CATTTAATGAGATAGCTGTTGATTTTTTTCAATCACCGTGACAGGTGTTTTATATTAGGT
GTTATTCGCCAGACATCTAGTCCACCTGTTGCCAGATATGGAATTAATATTCACTTATTT
TGAATTAAAATTTGTTAATAAATTAATAAAACAAAGTCAAAGTTCAAATTATTAAAAAAG
TAAAAGAAATAAAATATATTTTATAGAGAGCCCTTACAAAACAGTACCAACATAATGAGC
TTTCCAAATTTTGAATGGGCAAAATAAATGAATAGGCATTTCACAAAAGAAGGAAGGGTG
GCCAATAAGTATATATTAATATAAAAATGGTTACTTGTAATAGGAATCAAAAGTGTTTGA
CTTATTGACTAAGAGTCAGTTTTTGTTTTGATCCCTGTTAGTCTATCCAGAAGGCATGGG
TCTTAATAAACACCTTGACCTCAACAGTTTACTGAATACAAGGGTAATTTCATATGCCTT
GCCTTCTTTAAGGGTTTGTTGTAAAGATTAAAATAAATACATAAATATATATAAATACAT
TTATATGTATTTATATGTAATTACATACAACTTGCCTTCTTTAAGGGTTTGTTGTAAAAA
TTAAAAGAAGTATATAAATATATATAAATACATAAAATAAATACATTCATATATGTATAT
GAAATCACTTTGCCAACTATGAAGCCTGATTCAAATATGAAATGTTGTTTGTTTTTCCCA
GAGCACAGGCTGCAAAGCCCTGCATTCTTTTCTTTGATGAATTTGAATCCATTGCTCCTC

FIGURE 14.11

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GGCGGGGTCATGATAATACAGGAGTTACAGACCGAGTAGTTAACCAGTTGCTGACTCAGT
TGGATGGAGTAGAAGGCTTACAGGGTAATAATTATAAATACAGAAATAGAATGTTATAAC
AAAATGTCATCATGTCATCAGATTTTGGTAAAAAAATGTTCTTTTTTCCTCTAGGTGTTT
ATGTATTGGCTGCTACTAGTCGCCCTGACTTGATTGACCCTGCCCTGCTTAGGCCTGGTC
GACTAGATAAATGTGTATACTGTCCTCCTCCTGATCAGGTGACAATTTCATATTTAGAGT
CCAAAACCCAACAAATGCTACACTCTTTCCTTGTGAGCTTTACTTCTGCCAGGTAATGGC
AATTGTCCTTAGAAGACCAGCTTTCTTAGGGAAAAGCTTTAGCCACTGTTTGCTCAAAGC
ATAAAAAGATTCTGAATTAGATGCAAAGCCTTTTTTTGGCCCAGTGCAAGTCTGAAAACT
TTGTAATCCTTCTGTGTTGGCTGATTGGGGAAAAAAAAATGCAAGAAACCTAATGTATTA
TATTTTCACATTATCTTCTGTTCAAAGATTACATACTTCCATTATCCTGTCAAAAAAAAA
ACTCTGATACAGAATCAAGCATGTGAATCGTAAGCATGTAAGCAGGTTTCATAGAGATAA
TTTTTCAACTCTTCCTTGTCCTGTGTTGTTCCAACTCTTATTCTCCAATTTAGAAGCAAA
CAAATAAATGAATGAAAGAACAGATAGACAAATGAATAGTCAAAGGTATAAAGTATCTGT
ATATATGTTACATGTAGCTATTATTTAAATTATTTAGATTTTCCTTTTGAAATACCTTCT
TGGCACACTTGCCTAAATCTAGAAAATAAGCACTGTGTGAATAAGAAATTATTTACACTG
AATATTTTGTAGGTTTTTGGGTTTTTGTTTTTCAGACAAGGTCTCACTTTGTCACCCAGG
CTGGAGTACACTGGTACGATCACAACTCACTGCAGCCTCTATGGCCCAGGCTCAAGCAAT
CTCCCCACCTCAGCCTCCCGAGTAGCTGGGACCACAGGCACACGCTACCATGCCCAGATA
ATTTTATTATTAATTTTTGTATAGAGATGGGGTCTCCCTGTGTTGCCCAGGCTTTCTTGA
ACTCCAGGGCTCAAGTGATCCTCCCACCTCAACCTCCCAAAGTGTTGGGATTACAGGCGT
GAGCCACCATGCCCAGCCTTAAGAGTGTTTGATTTTCATTCATTTTCCTATATATATTAT
TTCTGTTGGGGAAAAAATTCCAAGGAAGATAAATAGTAGGCTGTTGGTACATTTCTCAAC
TTACTTATAAAGCTTTTTAGATATATAAGGTTAATTTATGAAGAAAATCATAAGATACAC
AATTTAAGATAATATTTTTAATTTTATTTTTTATTTGTTAAATAAATTTTTCTCCTTTCA
GGTGTCACGTCTTGAAATTTTAAATGTCCTCAGTGACTCTCTACCTCTGGCAGATGATGT
TGACCTTCAGCATGTAGCATCAGTAACTGACTCCTTTACTGGAGCTGATCTGAAAGCTTT
ACTTTACAATGCCCAATTGGAGGCCTTACATGGAATGCTGCTCTCGAGTGGACTCCAGGC
AAGTTATATGAGGAAGTTGTTATGACATTTTATGAGTGATAAAAGAAGTACAATGTCAAA
ATTTCCACCTTAAAAAATGCTATTTTTTAAACAACTTTGGTAAAACTGTATAGAAACATA
AATTTACCTTTAGTTGAATGTTCCATAGTTGGAATATGGGTTTTGCAGAGAATTTATAAT
TATGAAGTTTGATGTCTGTTTCTTTAACATTACCTTAATATTGGCAAAAACATGTTGGTG
TTTGCAAGGATATTATTTAAATTGGGATACCATGAATTAAATACTACAAACAAAAATAAT
TAGAGTTTTTTGTTTGTTTGTACTTTAACTTTTAAAAAATAATCAGTTAAAGTTGTTGTT
TTGAAGCTCACATTGTTCCAATCTGGCCAATAGGAGCCCCTTTTGTATGGCTCCTGTATC
TTTATGACATGTCCTCATCATTCTTGAATCACTTCCTCACTTCCAGATACAGTAAGTTAT
TCTTGGCCAGGTGCAGTGGTTCACGCCTGTAATCCCAGCACTTTGGCAGGCCAAGGCAGG
AGGATCATTTGGGCCTAGTTTGAGACCAAATCATGGTTGCACAAACTGTACCCACTATGG
ACAACAGAGTGGGATCTTGTCTCTGTGAAAAATTTAAAAATTAGCTGGGCATGGTGGCAC
ATACCTGTAGTCCTAGCTTCTTGGGAGAGGCTGTGGCAGGAGGATCGCTTGAGTAAATCC
AGGATGCAGTGAGCCATGCTTGTGCCACTGCACTCCAGCATGGATGACAGAATGAGACCC
TGCCCCCAAAAAAGAAAAATATTCTTGGTTTATCTTGTACTTTCTGTATCCCAGCCCTAG
CATCAGCCTTTTCTCTAAAGACAGTATTATGATTTTAATATTTACAGTAGATATTTGAAC
TGTTACATTATAGACTTTACCATATATTTTCTAGGAAGGATTATTCTATTACTCTTCTTT
ACCACATTTGTTTGGAATGTCTACAGAACCTACAGTTTCTAAATCAGAAACTCCCTAGGT
TTTTGCTATTTTGGCAAGCCATTGAAGTTCTTCCCTCTCCCTTTACTACCAGAAAGGTGT
GTATTTGTAGAGCTCTCTATAATGAGAAAGCACTCTATAACATGGTTGATTCATCATTTT
GGAGTAGAAAAGTATGAATGGAAAGTCAGAGACATAAAAATAAAGCCCAGAGGTCTGAGT
CTTAGCTTCATTACAGACTTTCTTGGGGGATGGTTGGTAAATTATCTACACATTCTATCT
TGTCTTTATAATTTTAATAGTTAAATTTTTACCATGTGCCTCAAAACCGTTAGAGAATTA
ATGAGCTCTTTGAAAAATGCTTCTAAGTTTCTTGTATTGCTCTAATAGAATGCTATCTAT
GTTATTATTTATTTCTGAGACTAAAATTGTTTACATCTTTAAACTGGTTGTCCTTTTGTG
TATTTTAGGATGGAAGTTCCAGCTCTGATAGTGACCTAAGTCTGTCTTCAATGGTCTTTC
TTAACCATAGCAGTGGCTCTGACGATTCAGCTGGAGATGGAGAATGTGGCTTAGATCAGT
CCCTTGTTTCTTTAGAGATGTCCGAGATCCTTCCAGATGAATCAAAATTCAATATGTACC

FIGURE 14.12

GGCTCTACTTTGGAAGCTCTTATGAATCAGAACTTGGAAATGGAACCTCTTCTGATTTGG
TATCTTGTGCAGTCATCATTATACAGTTCTGAAATATAAAGCTATATGTTGGTGTAAAGT
TGCAGTGATTTCTCTCCTAACCAGCCCCACATATTCTTCCTGGTTGGTTGGTTCTTCAGT
AAAATAGTCTTGTTTCTTGCTTACACTAATTGGTAATTTGCATTCCTTGTTAAGATTTTC
AAGACAGGGCTGGGAGCAAGGAACCAAAGTAGCGCGTGGTTGTGATTACCTTTGGTTTCT
TTGAGGTTTCTCTTACCTAGTGGCTTTAAAACATCTTTAGGAGCAGTTCCATTTTATAGT
AAACTTAAATTCTGTTATCATGAACAGTTGAGGATAATGAATAATTTGATACAATAATGT
AAGAAATTCCTGAAAACAAAGTGTTATCTGTGATACTTTTGCTGCATAGTAAGCACAATG
AAGTGTACTGATAATGTTTCAACAGGAAAGTGTTTTGATTAAATGTGGGCAGTATCACTG
TTCTACTAGCATTCAACATCTCTTCTAAAAATTAATAGTGGTTCACTGTAATTTTATTGG
TACATGTAACATCTGTACATGTGTTTGGTTATCTATATGTTTCCTGGTTTTTTGTACATT
TGCTTTATTAATTTAGGCTTTTTTTTTTTTTTTTTTTTGAGACAGTCTCACTCTATCATC
CAGACTAGAGTGCAGTGGCACAATTATGGCTCACTGCAGCCTTGACCTCCTGGGCTTAGG
TGATTCTTCCACCTCAGCCTCCTGAGTAGCTGGGACTACAGGCACATGCCACCATGCCCA
GCTAATTTTTGTATGTTTTGTAGAGACGAGGTTTCACCATATTGCCCAGGCTGGTCTCAA
ACTCCTGGGCTCAAGCTATCTGCGTGCCTTGACCTCCCAAAGTGCTAGGATTACAGGTGT
GAGCCACTATGCCTAGCCTAACTCAGACTTTAAAAATATAAAAGCAATTCATTTTTATTC
CCAAGAACAGTAAGGTGGTGGTTTAATTTTAGTCTTTAATTCTGTTTTTAATTTATTCTA
TTTAGAAATGTCCCAGAAACTTAGTATAACTTTACTTTCTGAAAATGAAGAAACCTGTCC
TTGGGCATTAGTGTGTTGGATTTAAGCAACAAAGTTAAAAAAACCTACCCTGTGTTATGG
CAATTTTCACTTGATGGTGGTTCTATAACACAGGTATCAGTGAACCTTTATAAAAGATGA
ACAACTTTTCAGCTTGCTTAATTTCAGTTAATTAACATGTATACTTATCTATGTTAATGT
TTTATTGCTTAAAATGTTTAATTTTTATATTTGGTAAACAGATAGTTTTTCTCTCCCCC
TCTTCCTTCCATCTTTCATTACTACAATTTACCATGCAGAGCTCACAATGTCTCTCTGCA
CCAAGCTCCATGACTCAGGATTTGCCTGGAGTTCCTGGGAAAGACCAGTTGTTTTCACAG
CCTCCAGTGTTAAGGACAGCTTCACAAGAGGGTTGCCAAGAACTTACACAAGAACAAAGA
GATCAACTGAGGGCAGATATCAGTATTATCAAAGGCAGATACCGGAGCCAAAGTGGAGTA
TGGCTTTTTCCCCCTCATTATAATTGTTAAAACTTCTTAAAAATTGTTTCACCCTTTTGA
TATATATTTCTTTGACTTATAAACGAGCTATATTTATAAACAAGGGACCAGAACACATTA
ACTCAGTCATGGTTATGTGCTTCCTTGCTTTCAATGTTTCATTATCTTATAAGGAAGAGA
ACGTATGGTCTCTTGAAAAAACTGACAATAAGAAGTAACAACTGGACTACCACATTTTTT
TTTACATCCTTAATTTAACTCTTCGTCAATTTCTTTTTTTACTTAAGGAGGACGAATCCA
TGAACCAACCAGGACCAATCAAAACCAGACTGGCTATTAGTCAGTCACATTTAATGACTG
CACTTGGTCACACAAGACCATCCATTAGTGAAGATGACTGGAAGAATTTTGCTGAGCTGT
AAGTAACAGATTCTGTTTTGGAAGTACAGCTACTATTACAAGTGACATAGTATTACACTT
AAACCTTTAAAGTTCGTGTTTAAAATAAAAATATTTTGAATATTTAAAAGCTAATTCAAA
AAATATGTGTCGTAGCTATGCATTAAAAAACCCCAAAATGTCAGAAGTACAGAAGTCAAA
ATTGAGTTTTCATTAACCAGTTCATTTGATTATATTTGAATTATTCATAATGGACTCATT
TAATTTTAGTAACTTTGGGCTGGGTGCTGTGGCTCATGCCTGTAATCCCAGCTCTTTGGG
AGGCCAAGGCAGGTGGATCACCTGAGGTCAGGAGTTCGAGGCAAGCCTAACCAACACGGG
GAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGTGTGGTGGCATGTGCCTGTAG
TCCCAGCTACTTGGGAGGCTGAGACAGGAGAATTGCTTGAACCCAGGAGGTGGAGGTTGC
AGTGAGCCGAGATTGCACCACTGCACTCCATCCAGCCTGGGCCACAGAGCGAGACTGTGT
CTCAAAAAAAAAAAAAAAAAATTTAGTAACTTCGAAGAAATAAGAAGGAAAATTAAAAGT
TGAAAGTGATTCTAATGTATAGTTTATAAAATTTTGTTATAAAAATACCTGTTTTGCCTT
CAAAATAATTTATATTAATATTTTATTGACCTCAAGAACATTTAAATACATTCAGATTTA
TTCATTTGTGGACCACATTTGTTATACATTGGATTTAAAGGATCCTTGCAATTGAGTTTA
TGGCCACCTATGCATCTGAGACCCATGGACTGGGAACCATTCTAGGTCAATGATTCAGTG
TGATTCAATTTAAGAGATGTTTATTCCTGGTCTTTAGAAGCTGCTACCTTTTGTTATCTA
ATTTTGCAGTACTTTGAAGTATGTATGTATGTGTACATACGTTAGTGCTATGTATTTATT
AAAGAAGAATCAGAAAACAGAGGTAAGGAAAAATAAGGAAACAAATTTCTGTTAAGCCCA
CCACCTCCCAAAGCATATTTGTTTATATGCTTATATATGTTTTCCTATTATGGTAAGAAC
AGTCTGTACATATTGCTATATAGCAGTCCCCCTTTATCCACATACATCCTGAAAATTGTT
TTACATTTTAAATGTTAACTACTTTATTGTTTTTAAATGTCATTTTATAGTGTAGCTATG

FIGURE 14.13

CCACAATATCCAATTTTTAGACATTTAAATTGCTCCCAGGCAATGTGGTAATGAACATTC
TTGCAGCTGAATATATGCACATATCTAATTGTTTCACTAGGATAGAGGTGGAATTGTATA
ACAGGGAGCTCACATTTTTTAAGGCTTTTGAAATGTATTGCCAAATTGCCTGCCAGATAT
ACTGCACCATCACTAACATTGTGTGTTGCAGTATTTTTCTAAACTTGGCCCTTTTGATTT
TAGAAAAATGATATCAATAATTTACATTTCTTTGATTAAAGTGTAGAAGTTATAATTTTT
CATATTATTCATTGTCATTTGTATTTTATCTTTTCTAACTTGTCTCTTCATCCCCTTTGC
TCCGTTTTCTATTGGAGTGCAACTTTATTTGTAAGAATTCTTTTTAATTTCTGTGACTGG
AATTTTTTTTTCTAGTTTGTTATTTCCCGTTCATTTCTTAAAATATAATTGTGTTTGCCA
ACAATCCATTATCTTTTGTTTTGTAATGGTAGTATTTATACATATTAAATTATCTCTTTC
TTTTTTCAGATATGAAAGCTTTCAAAATCCAAAGAGGAGAAAAAATCAAAGTGGAACAAT
GTTTCGACCTGGACAGAAAGTAACTTTAGCATAAAATATACTTCTTTTTGATTTGGTTCT
GTTAAGTTTTTTGATGGCTTTTCCATATGTTGTAACAGGAAAAAAATGGTGTCTATGAAT
TTCTTCTTAATTTAACAAATTTGGTTAATTTATAAAATCACAGATTGGTAAATGCTATAA
TTATGTAATGATCAGGATTGAGATTAATACTGTAGTATAAATTGGGACATTATAACAGAT
TCCATATTTTATTTCCTAAAATCTAAATTCAGTCTTTAATGAAATAATATTAGCCAAATG
GTGGAACTAATTTATTTCTTTTGAGGAAAAGATAATAAAGAATGTAATTAAATTTAAATT
TCTTGGAATTCCCAGTTGTATATTCATCACCTTTGTAGCATTTGACAAATTTTATGCTTA
GCAGCTTCTTCACTGTTTTGAAATAAAATATCCTATTACCTACTGATACAATTATCTGTT
CTTTGTATATCAAAAAATGTGAAATTTACACATAATTCAAATACATTTAATTATCCGCTC
AACCAGAAATGAAATCACATCCCTCTACTATACTACATCCAGCTCCAAGCCCAAGATATT
TAAATGACATCCATTCCTCTCCTAGTTCCAGTTATGATTTTATCTTGATATTCTCTCATA
TATGAACTAAATTATAAAGTTAGCCACCATCAATACAATCTGCGTATCTAATATCTTAAC
TATATAGTAATGGGGTAAGGGAACAGCAAAAAGGAGAACATTAATTAAAATATACAAGTA
AGCCTGGGCAACATAGTGAGACCCCATCTCTTAAAAAAAAAATTAGCCATGCATGATGGT
ATGCCTCTAGTCCCAGCTACTTGGGAGGCTGAGGTAGGAGGATCACTTGCTCCCAGGAGG
TTCAAGGTTCTAAACCAGCAAAGCTCAGAATCCCAGGGGATAGAAACAAAGACTTAGTGG
ATCACTAGTATTAAACTGAGACACGTCACCCTGCATTGCACTTTGTTTCTCAGTTCTTTG
ATGAAATCACTGAGCTGACATACCTGCCCTCTTTTCACCATAAAGTGAGTTTCATGATCA
GAAGCAATGTCTATGGGATAGCCTAACAAACAATGTAAAAACCATTTAGTAAGTTCATGA
AGGGTGGTGGTGGTAAAAATTTGGAGAACATACAAAACAAATACAATTCCAAGGTGTGTC
CCCTCCAGGAAGGACAAATTGCTGCCTGCTCTGTGATAGAAGAGGATCAGATGTAATCAA
CCTGCCGTCAGACTTGGGCTGTTCTCTCCTGGGTGTGGACTTGCCTGGTTGGTCACTGCT
GCTGACAAGTAGGCTGTCAATATAGCTGGGTTGTCATGTCAGCTGTGGTGAGGGGGAAGT
CCACATTGTGGAGGCCACATCCCTGCACTCTTGGCCAATTTGACCATGAATCTTAAGCAC
TGGGGTGGCTGGAAAAGACAGCCGATTGACATCCATACAGAGGTCATCTTGACCACTTGA
TTAGTATAAGCACTGAAGGCTTTTAACTGAGCATTCACATAGGACACAAATATTCTGATT
CTTTGGGCCCATTCCAAGAACTCTGGGCATACTTTTCCTCCAGACCTCATACCCAGTTGT
GTTCTTTCCAAATTTCTGGTCATCTGGTTATGTTATTAGCCACTATCTGTGAATCAGCAT
AGATTTTTATATCAGACATCTCTACCTCCTGACAGAATGGAGGAGATATGTTACTTAACA
ATTCTGTTCCCTTGGAAGATTTCCTGTCTCCACTGTTTGTAAGGGCTACTCCCTCAATGT
AGCAGTAATGCTTTCACTCTGATGGGAAGTCACAGTGGAATTCTGGGTCTCCAAGAATTA
GTGTTAGTGCATACACAGTGTCTGATAATCCCCAGAGTGTCTGGTGCCCTTGGATCCTGT
GAAGAAGGCTTGGAGAAAAGAAGATTCATGGCAAGAACTTGTGATGTGATGACAGGGCCT
TTTCTCTGGCTCTTCATTCTTAGTCTGACCTAGGTGTGAGAATTAGGTCAGGGGCCATGA
CTATATTGTGGTGACTCAAACCAGGCCTTTGTTTACTAACTGGGAGATTTTTACATTGTA
AGAATCAAGTAGGATCTTTGCCCATGTATTTTGGTCTTAAGAACACAAATGATATGGCTC
CAATGACTGGAGGAACACCAGGGTCCTTGGTCTCACGCTGATTTAGATAAAACGAC*TGTC*
AGGCCTCTGAGCCCAAGCTAAGCCATCCTCCCCTGTGACCTGCACGTATACATCCAGATG
GCCTGAAGTAACCAAAGAATCACAAAAGCAGTGAAAATGGCCTGTTCCTGCCTTAACTGA
TGACATTCCACCATTGTGATTTGTTCCTGCCCCATCTTAACTGAGCGATTAACCTTGTGA
AATTCCTTCTCCTGGCTCAAAACCTCCCCCACTGAGCACCTTGTGACCCCCGCCCCTGCC
CCTAAGAGAAAACCCCCTTTGATTATAATTTTCCACTACCCACCCAAATCCTATAAAATG
GCCCCACCCCTATCTCCCTTCGCTGACTCCTTTTTCGGACTCAGCCCGCCTGCACCCAGG
TGAAATAAACAGCCTTGTTGCTCACACAAAGCCTGTTTGGTGGACTCTCTTCACACGGAC

FIGURE 14.14

AAGCTTTAGTAGAGATCTCAAAAATGGTTGGATGGTAGCAAATTACTAAGAACTCTCAAA
GTTTCTAAAGCCTTAGTTTCAGCTTGCTAGAAAACCTATGTTGAGTATTATGGCTAGTTC
CATAGTTGAGTTGGGAAATGTCTTTGAGGAGACACTTTTTCACTTTGTATTCATCTGTAC
ATTTTCTGTTACTTGCATTCTGTCATGCTCAGGCTATTAGAGCAGGTACATTTTTATAAC
TGGAATGTTTATGTGTAGTGAAGCTCTGAGAGGACTTTGCATTAGATCTCAGCAGCATAA
TCAGAAGGTTGTCCTTTGTCTCAGCAATTTTTAAGCTAATAGTAGCAGAAATTGCAGTGG
AAATAGACTGCTTTGCCACAACATTCAGAAAATCATTTATCTTTTTATTGCAGTTCTTGT
CACCAAACAATACATTTTAGTACTTCTCAAATTGCAGAACTCTCATAGGGCTGGGAAAAT
GCCTGTAGACACATACATACTATGAATGTGCTAATGTTTTTTGTATTTTCATAGCCCATC
AAAGCTCCTGAGTCAGTTTCCACTATAATCACTGCAGAATCAATCTTCTACAAGGTAAGC
TTTTGTAGAGTTACTGAAGGAAGAGTTGGGCCTAGTGGGTAATGTGCCACTAAAATGTTG
GATTAGTCTAAAGGTCTCTGCTACTCTTTATTTGTATAAGGTGTGATTATACTTTTTGTT
CCCTTCTTAGCTGTTTTCCCCCATAAGTGGCTGTTATTAAAACATCTCATCTAGAGCTGA
AGTGGGAGGAGAAAGTGCCTACTGACACATGATGTGAGGATCTTAAGTATTTTTTTTTAG
TGTAGATTGTAGGAATTATTCTTAAAATGCTGATTGTATAGTGTGGAGCCATGGAAGACT
GAGCCGTTAGTGCGATGGCATTGAAGAATGAGAAGGACAGAGACAGGATTTGGACTAGTA
GAGGTTGTCGACTGTGGTGTCAAATGGGTAGAGTAGGCCCAGAGATTCTAAAATGCCTTT
AAGTGGAGTTGAGCTGAGTAAGGGCAGTAGTGAGGATTAACACCTACTAGAAATTCATAG
TGAGAGGAATTCCAAGATGTTTTGATAAAAGAATGAGGAGGTCAGGTTTCCCAGGGCCAA
AGTCCATGAACATCTGATACCTCAGTGAGAGAAGTGACAGATTGTTGTGTTTAAACCAGA
AGTCTTAGGAAAGGAATTAGAACATAGACCCCCAAGGCTCGGCAGGCCTGGCACGGCACA
GGCAGCAACCATTGAAGGCTATTTGGTGTTTCGGGATCTGAACTGTCATTTAGGGGACAG
TGGTGTGAGTTAGTACTTTATACTTGACCCAGGTGGACTGAGAAACTCAAGTGATGATGC
CCTTAAGTATACTTTTTTTTAAGCCCACAATCTATATAGTCGAAGTCTGTTCCTCCCAAC
AGGGGTACACTGGCATTCCTCAGCAGGGCTGGGAAAAACCAACAACAAAAAAAGTCTGTA
CACAGGCAAACATCTCTCTTATTTTTCCAACATTTAATACATTGTTAATAAAATATCTAA
AGTTTAGCAAACAGTTGCTGTGTATCAGTGGCTGAGCATTTTGCATGCTTTATTTCATTC
AGTTCACTCTATGAGGTGGATACTACTATCCCCATTTTCTAGATGAGAACATTGAGGCAC
AGCGAGGTTAATTAACTTGTCCAAGATCACATAGCCAACAAGTCATGGAGTGAGGCAGTC
TCATGCCAGAGCTTAAGCCTAGAGCATAGTTCCTGGCTCTACAGCTTTAGCAAGTGACTG
GCTATGTGACGAGGACCAACCTCTCTAATGTCTCATCTGTAAAATAGGAATTGTAAATAG
TTACTACCTCAGTGGGTCAAATGAAATCATATGTGTTAAGCACTTAGCAGAGTAAGCACT
CAATGAATAGTAGGAGTTATCACATCTTCGTATTTGTGCATTACCTTCACAGTTTACAGA
TTAAGGCCAGAAGCAACTTGTTGAGCTACGGGTTTAGTGTACTAACAGTTTCCATGTGTG
TCTCCATGGAAGGGTGTGTGGGACCTGTTATTGTGACTGTCTGTACTTTCGTATTGTTGT
CTGCCACCCATGTTTATTAAATGATAAGGACAATAATGCAACAAAGTAGTCAAGTAATGT
TGCAAATGCCCAGTATTGTAGTGGCTATCACAGCAGTGCCACTGGCAGGCAGCACCATGG
TGGCAAGTTCAAGAGGTCACTGCCAGCCACTGAGCTAGAGCCCAGATCAGGCATGCAAGA
GGAGCCTGAGTGGGAGCCACTGGGGATCACGGCCAAGAGTGTGACCACCCAAGACCCAGA
ATGGCTGAGTGGCCTCCCTGGAGCATGGCAGTGGCAGAACAACTCCATGAACTCAGATCT
GGTGATGCCTAAACTAGTGCTGTTCTCGTGTGGACCCCTTTTCTCTACCAGAAACCTTGA
ATCCTCTCAGCAAATGAGGAGACTACTCAGATCAGTGACTTAGTCCTGTTTGGTGTTATA
TATGTGTACACAACACAGCACATATTAATAAATACCTACTATGTGCCAGGCACTGCCTAC
CACTGGAATCTTTCACTAAGACATTGTTTTTACTTTGCATTTCTGCCTTTACACTATGAA
AGTAGATGTTTTGGATTCATATTCATTCAGCATACATTTGAATATGCTGTGTTATGCATA
GTAAGCCTATGATAAGCAAGTATTCTCATTTAGAATTTGGGAATATTGATTATACATGTG
GACAAACAAACCATAAATGCAAACTATTTATATGATAAATAACTTTGGACTGATGGCTGG
GAGGAAGGACCAGCTATTGATGGGTAGGAACTAGCAAGTAGCGGACTGTGGCCTGCATAG
ACCAGACCCATCCGTAGTGATCCAGATGAAACAGCCACCCTCAGACACTTGGATAAAGGG
TCCACCAGGAAAAAACTCCTGGCCTATCAGGTGCTATGTTACAGTTCAGTTACTGGAAGT
ATTTCCTCAAAAGTGTTTTTATGGTTGAGGTACACATTCCTACAGCTTTACCTGCTGCCA

FIGURE 15.1

AGTCCCTGTTTCAAGGGAAGCAGCAATGAATTACACTGTTCCCGTAGTCAAGGACAGTAT
ATCTTACCAAGAACTATACCCACTTAAGGAGGTGCTGGATGTCATAAAGATTTGGATCAA
CCATTATGGGTGTTCAGAGGAGAGATTATTTCCAGCTCAAGACCCAGGGAAGAGGACATA
GGATGGATACCAGAGTCATAGGGAGGATTTAACACAGGACATGTACACATTAGTTAGTTG
GGTATAAAGTGGAACAGAAATGAATGAGACACAAAGCCTTGAATGCCAGAAATACTAGTA
GTCCTGTTGTGGAAGGATATAAAACTCAACTGGGAGTGGAAGAGAAAGGCAGCAGTGAGT
CTAGGAGATGTACAGTAGGTTGAGGTAAACATATCCTGAAGACTATAATCCAAAGATTAT
TTTTGGTTTGAATTTGTTTTGGTTTGAATTCATGGTATCTATTTTCTTTGAGTGGATGGT
TGGGGAGGGTGGCATGTAGAATGCATTCTTACCAAATCAGCATGATTTTCAAGACAGTAC
AGAGAAAAGACTGCTGAGCTGATGTAGGAGCTTTGGCTGCAGTCTCTATGGCTTTCAGCA
AGCCGTTTAACCTTACTACTGCTTCATGACTGTGGCTAACAAAGTAGGGATAGTACGGAG
CACAGAGGATTTTTAGGGCGGTGAAACTATTAATACTCTCTTTGTATGATACTATAATGG
TGGGTACATGTCATTATACATTTGCCCAACCCCACAGAATACACAGCACCAAGAGTGAAC
CCTAATGTGAACTCTGGTCTTTGATGATGCTATGTCAGTGTACGTTCATCCGTGTAACAA
GTGTACCACTCTAGTGGTGGGAGGGGTTATTGATAATAGGGGAGGATGTGCATGTGTGGG
GGCAGGAAGTATATGGGAAATCTCTCTACTTCTGCTCAATTTTGCTGTAAACCTAAAACC
TCTGTAAAAAATAAAGTCTATTTTTTAAAAAGTGGGGATGGTATTACGGCAATATAAAAT
CAAAATACTTTATGAACAAATCTTTTCTCCAGATGTAAACTGTCATATATGCACCCTCGT
ATGTGTATGTATAATTTTCATTCAAACGTGAAACAACTTTAGAATTGGCACCAAACATAT
AAACACTGATACATTAGACTATCTCGAACACCTTTTACTGACCACTTTGAAAACTTGCTT
ACCTATTAAGGTTCATTCATAGCTGTGATGTTCTATTTTTATTTTCAATGTGGGATTATC
TTCTGTTTCCCCCAGGGAGTATATTACCAAATTGGTGATGTTGTTTCTGTGATTGATGAA
CAAGATGGAAAGCCCTACTATGCTCAAATCAGAGGTTTTATCCAGGACCAGTATTGCGAG
AAGAGTGCAGCACTGACGTGGCTCATTCCTACCCTCTCTAGCCCCAGAGACCAATTTGAT
CCCGCCTCCTATATCATAGGTAAGTTTGACAAATGGCACAGGTTTTTTTTTAACTTAGTT
AACTCTCCAATATTATGTAAAAGAGTGTGTTAGTCAGCTTGGGCTGTCAGGACAAAATAT
CACAGACTGAGTGGCTTAAACAACAGAAAGTCACTTTCTCACAGTTGTGGAGGCTGAAGT
CCAACATCAAGGTGCTGGCAACACGGATTTCTGGGGAGGCTTTTCTTCCTGGCATATAGA
TGGTCACCTTCTTGCTGTGTCCTCACATGGCCTTTCATGGAGTGAGAGCTCTTTGGTGTA
TCTTCTTATAAGGACACCATTTCTGTCAGATGAGGGCCCCACCCTTATGGTTTCATTTAA
CCTTAATTGCCTCCCTAAAGGTCTCATCTCCAAGTACCATCACATTGGGGATTAGGGCTT
CAACATATAAATTTGGAGGGTGGCGGGGGGGGATGCAATTCAGTCCATAACAAAAAAAGC
ATGAGTATTATTAAGTACAAAAAAATTAGAGAGCTTTATAGAAAATATGAGGCATTTTAT
GTAGCTGGAGTGTGAGTGCTATCAGTTATTTGAGTTAGAGCAATGTGCATCTACTAAGA
AGTGGTATGGATAAGATTTTTTTGGAGTGACCCAGGGTTAAACTGTACTACAAGAATGTA
TTGCTCAGGAACTAGGTTATTTAGGTTACTTATTTATACAAACCTATTCAAAAATAATTT
AGGAAAGAACTATCCCAGTTATCCCATACTTGCAAATTCTCAATATGTGTGCCTCTGCAT
GCTACACATGTCATCTTAGGCCTTTATAGTATAAAGGCTGATAGTTGAAATGGCAGCTGC
TGTGCTTTTGTTAATTTCAAAGCTGCCAAAACAGTTGTGAGATAGACTCACAAGAATTTA
CTGATTAATACAATTTTTAAAGTTTTCAGATTTTTACAGTTACTTCAGACTTTTTATCTT
TCTGCAGTGAGCATGCATCATTACTTTTGCATCCTGAGAACAAGCATAAGTGTGTTTTTG
GAGAGAACTCCAGGGACAAATAATATACCACTGTTATTCTCACCTATATGTCAAGTTTGA
TACATTACCAAACAATTCTAGCCTTCTGCTTATAAGTATATAGAATTTTTATTTACCTTA
TCTATGGATCAGGATCTCAGCAGAGGCAGTGATGTATCAGAATCACCTTCGGGATTCCTC
TACTGCCTCCTCTTTCTAATCCCCAGATTCTGATATGCATCCTTGTCCTACAGCGAGGCA
GCATGGCATGAGGTCAGAACACCAGTTCTGGAGCCAGACTGTCTAGGTTCACAGCCTGCC
ATTTACCGGCCATGTGACTTTGGCAAGTTTCTTAGTCTCTCTTGCCTCACTTTCCTCATA
TGTAAAATGGGAATAATAATAGTGCCTACCTCAGAAGGTTGATGTGAGGAATGAAGGTAT
TGATACATGTAAACTTAGAGCAGTGTGGGTACAAAATAAACATGATGCAAGTGTTCAATC
ACTGTTTTTGGGAGAATGCCATATTCTTTAAGCCGTTAAAGAAGAAAAAATGATTAAGAA
TAATTTCAAAGTAATGCATGTTTCAAGGGCTAATGCCAGGTTGCTCCCAGAGTGGTCTCT
CCCAGTGTCTAGAAATTTTAACATCTTATGAAAATGATATATATGGTCAAAAATGTATTT

FIGURE 15.2

AACCTTTCCCTTGGCTGCCTTCCAGGGCCAGAGGAAGATCTTCCAAGGAAGATGGAATAC
TTGGAATTTGTTTGTCATGCACCTTCTGAGTATTTCAAGTCACGGTCATCACCATTTCCC
ACAGTTCCCACCAGACCAGAGAAGGGCTACATATGGACTCATGTTGGGCCTACTCCTGCA
ATAACAATTAAGGAATCAGTTGCCAACCATTTGTAGTTCACAAATTAAAACTGGGTTTCC
AGGCCTGGTGTGGTGGCTCACGCCTGTAGCCCCAGCTATTGCACCACTGCTCTCCAAGCT
GGGCAATGGAGTCAGATTCTCTTTCTTAAAAAACCACAAAAAAACTGGATTTCCAGTTCT
CTAATATTCTTAGTACCACAAGATATGTCATAGGTATCTTTAAATGAAATTCTTAGCTGG
AAAAGTGACTAAAAAGTTTTTCTCCTGCTACCTAGTAATAAACAAATCATTGTTTATTAC
TGGTCACTTAGAAAATTAAAAGGGATAGGGCCAGGCACAGTGGCTTATGCCTGTAATTGC
AGCACTTTTAGAGGCCGAGGCAGGCGGATCACCTGAGGTCGGGAAGTGGATCGCCTGAGG
TCAGGAGTTCGAGACCAGCCTGGCCAACATGGCGAAACCCCGTCGCTACTAAAAATACAA
AAATTAGCCAGGTGTGGTGGCATGTGCCTGTAATCCCAGCTATTTGGGAGGCTGAGGCAG
GAGAATCGCCTAAACCCAGGAGGTGGAGGTTGTAGTGAGCCAAGATTGCACCGCTGTGCT
CCAGCCTGGGCAACAGAGTGAGACTCTTGTCTCGGAAAAAAAAAAAAAAAAAAAAAGGCTG
GGCACAGTGGCTCACGCCTTTAATCCCAGCACTTTGGGAGGCTGAGGCAGATGGATCGCC
TGAGGTTGGGAGTTCGAGACCAGCCTGGCCAGCATGGTGAAACCCTGTCTCTACTAAAAA
TACAAAAATTAGCCAGGTGTGGTGGCGCACACCTGTAGTCCCAGCTACTCGGGAGGCTGA
GGCAGGAGAATTGGTTGAACCCAGGAGGCGGAGGTTGCAGTGAGCAGAGATCGTGCCACT
GCACTCCAGCCTGGGTGGACAGAGCAAGACTCCGTCTCAAAGAAACAAACAAAAAATTAA
AAGGGATAGAATATAATGAAATATATTTTGAACTTAAATTATATTCTATATGTGTATCTT
CCTAGGCAAAAGCTGTAATTTCCAGAGAGACCATTAGGAACAGGTAGTATCTATTTTTCT
CCATTATTTATTTCTAGAAACTCATAAAATGGATTGTATTTTTCTATAAGAACAAAATAT
TAATTAAGGTATAGATGACTGACCAAGGGCTTAATCAAATAAAATGACTAACAGCATCTA
TCATAAAGCCACACAAGCCTTATGTTCTCATCTCAAAAATGCTGTGACAGCTTTTTGGCT
GCTTTAACCATAAGAAAAATGATTGGTGGATGATTTTATTAGCCCAGGCTTTTAAAAACT
TTCATCTAGGCCACGTGCGGTGGCTCATGCCTGTAATCCCGGCACTTTGGGAGGCCTGAG
TGGATGGATCACTTGAGGTCAGGAGTTCAGGACCAGCCTGGCCAACATGATGAAACCCTG
TCTCTACTAAATATACAAAAATTAGTTGGGTGTTATGGTGCATGCCTGTAATCCCAGCTA
CTCGGGAGGCTGAGGCAGGAGAATTGCTTGAACTCGGGAGGTGGAGATTGCAGTAAGCCG
AGATCGTGCCACTGCACTCCAGCCTGGGTGATAGAGCAAGACTGTCTCAAAAAAGAAAAA
AAAGAAAAAAATTTTAATTTAATCCTTCTGTAGAAACAGGCATTCAGAACCATTCCATTGA
TCTTAATAAAGCTGCTCTTTACTGTTTCTAGTCAAAAATGAGACTTCGATCAAACCATAA
GATTTTATACTGCAGATAGTCAGCTTCACCAAAGCCGCAGAGGAAACATGTCGAGATCAG
GCTTCCTGCTTGATAGTCTCTTGACTACCATTAAAACGAATATTGGGAGGTCATGAAAGT
CATTGGTAGGCCATTAGCATTGATATCTTTAAAACATCTACCCTAAACCATCTGCTATGG
ACCCATAATAAGAGGCCTGTTGTATATGAAATTGTCTAGAATTCAGGTGCAGGTCTTTGC
CGGTTAAGTAAGGGAGCAACACGTAAAATGGGAGAGGAGTGGGGTGTACTCACTTGCCTC
CTCTTTTGTCCTGATTTAACCAGCATTTTTCAACCCTGGGAAAATTTGCAGAATCTAAGT
TGATTGTAATGATTTTGAGCTGCAGCAGCTTTAACTCTTACCCTTTTTCCACATAGTTAT
GGTGTTTGAGTTGGAAAGAAACAACTATAGGTAGCTACACGTACATAATTATCTCTTTAT
TCACAAAGGGTATAGTAAAATTGATTGTAAATAACTTTCTAAGTGCCAATATTCAAAACT
TTTGGATTAAAATGTATTTTTCACCGTGCATTTACTTTGGATGTATTTATTTCATTTAAA
CAATTTAAATGGGGCTCTTTAACCAAAAATGGTATTTAAAACCAAAACAGTATCGTACTT
AGAATTTGGAGTAGAGGCCGGGCACAGTGGCTCACGCCTGTAATCCCAGCACTTTGGAAG
GCTGAGGCAGGCGGATCACCTGAGGTCAGGAGTTCGAGACCAGCCTGGTCAACATGAAAC
CCCGTCTCTACTAAAAATACAAAAATTAGCTGGGCGTGGTGGCGTGCGCCTATAATCCCA
GCTAGTCTACTCGGGAGGCTGAGGCAGGAGAATCGCTGGAACTCAGGAGGCAGAGACTGC
AGTGAGCCGAGATCGCGCCACTGCACTCCAGTCTGGGTGACGGCATGACTCCATCTCCAA
AAAAAAAAAAAAAAGATTTTGGAGTAGATTCATCATTAATAAGTAACAGATTTTAGGAAA
ATCAAAAAATGGCTAATAAAATGAACACAATGTAAAACATTTATTAAAATGTAGACTTTT
AAAAATCTATAAATTGATCATCTGTTTATAAATTGGCAGATGGTTGTGTACCATCTTTTA
AAATAAAGATTGAATTTCACCCAGTGTGATGGTTCCCATTGCTTATATTTCTCCTGCTGA

FIGURE 15.3

GGCCGGACCTGATATGGCCCTGGTCTGTGTTCCCAGCCTTGTTTCCTCATTACCACTAAA
ATCTTTCCCCTGTATGCCCGCCCAATTTTTCTGGCTCTGAGTCCTTGTTCATACTGTTCT
CTCCAATTCTACCTTCCAAAGGCCTTTCTTAACACCTTCGGATTCTTTCTTTGAGAACTT
TCCAGATTCCCATGCCTTTTTGGAATCAATCTCTATCCTATTGTCATCACATTTAAGTTT
CTACTTCCATCATCCTCACTCCTATCCCTTTGGTCCTGGGATGACAGGGATGCTGTGTTT
TATTTACTCATCTTTGTAACTTCCACATAACCTAACCCCGGTTCTTGCTTATGGGAGATG
CTGATTGTAGGGTCTGAGTTAGATACTGTTAACTAAAATGCTTGTTGATATTTTAGTTAT
TAATTCATATTAACTTTGGCTGAAACTTTTAAATTCTATTGTGAATAGTCAAGTAAAATT
TAGATTGTTACATTCTGGGTTAGTATTAGATTGTTTTTAAGATTGTTTTAAACAAGATGT
TTTTAAGATGAGTTTTAAATAGTTCTCTTAACACAAATAAAGCTTAATATGAGTATTTGA
AGGAAATTATCCCAAACCATTCCAGTTCCTGGCTGTGAAAGGCTTTTCCAGGCCTAATAA
GTTTTCCACTTCAGCCGTAAGTAGGTGAAATCAAATGAACAATAGAGGGAAATGTATTTA
TTTGCTTTATACACATGCATGTGTGTTGTGTCTACATATAAACATTGCACACGCTTAGAA
TGAAGTTTCTGTCATGCCCAGAAAAGGGAGAGGCATTTTTGTGGATTTTGTCTGGCTGCC
CTGGGGATGTTTGAAGAACTGTGCTGTTTACTTCATACCAGGTGTGTGAGCCATACCTTT
GGTAGGAGGGTATACCTCCTACACCCAAGAAATATAAGCCAGGAGAAGGTCTGTGCCAAG
AGAAGGAACCCAAATGACCCACAAGAGGTGGGCCATTAATTATTGGGTCAGATGCATAAA
TGCACAGTAATTTATTTAAGCACCTCTTAATGGTGACCCACAAGGAAGATTGCTCGTAGT
AGCGGAAAGGTTCACAATAAATAAGAGAAAAAAGCAGAATGTAGAACTGTATGATAGCAA
TTCTGCAAACAAGAAGCATCTTTTATAAAAGATGGAAGGAGCCCAGGCACAGTAGCTCAT
GCCTGTAATCCCAGCACTTTAAGAGGCTGAGGTGGAGGATCACTTGAGCTGCAGTGACCC
ATGATTGTGCCACCACTCCAGCCTGGGTGATAGAAGTGAGACCTTCTCTCAAAAAAAAAA
AAAAAAAAAAAAAGACGGAAATTCCTCCAGAATTTTAACATGTCAACAGAGGTTTTCTGC
AGCTACTTTTTTCAGCTTTATACTTCGCAGTATTTTCCAAATTTTCTCTAACAAGCAGTA
TTTTCCAAATTTTTTACAATAAGCACACACACACACACACGTTTGTTTGCATAAGTGCCC
AACTGGTGGTGAACAACCGCTGGCTTTTAGTCTATACATATCTAGAATATTTTATAAATA
GTAGTTCTTAAACCCTTGAAAGGGAGTGAATGACCAGCTGAGAAAATAAAGTCAGTGATT
TCATTATTTTCCTATATTCACATCATGATTCTAGGAAAGAACTTGGGAGTGACTTCCTTC
AGCTTCAGCCACTCCTGGGCCAGGCGCATGCTTAGCTCTGTGGTAAAGGTCACCAGCTTC
TTCTGCAGGGTGCCTGTATCATCTGAATTGGAGGTTTGGCGAGGGTAAGAGACTGATGTA
GGTTCAAGTTTTTCTTTCCTGTCCTCCACTTGAAATCTGTCTTCCCTTCCAGACTGCCTG
CGCTGCTGACTTAAGGCCCCAACACCAAACACAGAAGCAACAGCCTTACACAGAGTGTTC
AGCAAGCTCCAACAATTGTGTAAGGTAAAGTTTCCTTTATAGATTCCTTTTCTATATCGC
TCCTAGTGGTTCTGTTTCTCTGATCGAATTCTGGCTGATAACAGTTGCTGAGACTCTGAA
AGAGAAGGCAAGGAACTACTGTTTCTCATTATAAACTGTTTAGAATTATTTGGCCATCTT
TTTGCTATGAATATGTAGTGCTTTGATACATTTTTTAAATCAAAAAGTAATGAAAGAGAT
CACATAGGGAAAGATAGATTGGATTATTTTTAAAGTTTATATACTAAATTGAAAAGCAAA
GAATAAAATGGGAGAAACAGCTCCCTCATGTGGCTGTTGGCAGGAAGCTTCCATTCCTCT
CTGTGGGCCTCCACAGGTTTGCTCACAGCAAATGGTCCGTGACAGAAAGACGCAAGGGCA
GTTGCACCCAAGATGGAAGCCACCATCTTTTCTATAACCTAATCTGAAAGAAGGACATA
CCAGCACTTCTGCCATATGCTGTTGGGTCACACAGACCAACTCTGGTACAGTGTGAACAC
AGGACCACACAAGGGCGTGAATTCCAAGGGCAGAGACCACTAGGGACCACCTCAGAGGCA
CAGAGGGACACCCTATCCAGCTGGTGGCCAATGTAAATTAACATAGCTTTTTAGAATAGC
AATATGTATCTATAATCTTAAAAGTATTAAAAGTACTTCTTGATCCAGTAATTTCATTTC
TAAGAATCCATGCTAAGAGGATTTAAAATGTGGACCAAAAAATGGGTATAAAAAGAAGTT
GTTAACAGTATTTAAAGTTGTGAAAAACCAGAAACAATCTAAAGGTCCAACAATAGGAAA
ATGAATTTTGATATTTTTCTAATAGAATTTTATGCTGTCATCAGAAATACCATTTACAAA
TAATTTTTAATAACGCAAAAAAAAGTTTATAAAATGTTTAGTGTAAAACCTGGACACAAC
TACATAATGATTCTGATTTTGTAAAAAAAAAAAACAAAAACACACACATATACACATGCA
TACATATGCATATAAAGAAAACTGGAACAAACAAAATAACAAGCATAGTTGGAATTACAG
TCATTTTAATATTCTTTATGCTTTTAAAAATTTTGAAGTTTGTATTACTAGCATCCACTA
CTTACGTAGTCAGGAAAAAAATACAACTTTAAAATAGATATTTAGGTCCAAAGATGGTAA

FIGURE 15.4

TCTAAATGGTGTTACAGGCTGAATGTGTGCCTGATCCCCATGCCCCAAGTTCATATGTTA
AAGCCCTGGCCCCCAAGGCAATGGTATTAGGGGAGTAGGGCCTTTGGGAGGTAATCAGAT
TTCTACGAGGTCATGAGGGTGGAGCCCGCATAGTGGAATTAGTGTCCTTTTAGGAAGAGG
AGAACAGACCAAAGCCTTCCTTTCTCTCCTCACTATGTAAGAAGACAGCCAGAAGGTGGC
CACAGCCAGGAAGAGAGCTCTCACCAGAACCCAAATCTGCTAGCACCTTGCTCTTGGGTT
CTCAGCATCCAGAACTGTGAGAAATGAATGTGTGTTGTTTAAACCACTCAGGCTACGGTA
TTTTGTTGCAGCAGCCCAAGCTGACAGAGATAGAAACAACACAAGGACCCATCAGCAGAC
GAATGGATGATCAAAACGTGGTGAGGTCGTGCAGTGGGATATTATTCAGCCGTAGAAGGA
ATGAAATTCTGATACATGCTATAATGATGAACCTTGAAAACATGTTAATGGAAATAAGCC
AAACTTAAAAGGACAAATATTGTATAATTCCACTTATATGAGTTAGTTACCTAGAATAGG
CAAATTATGTCATAGATACAGAACATTAGAGGTTACCAGGGTTGTGGGAAGAGGGGTATT
GTGGGTACAAATTTTCGGTTTGGAGTGATTTTGAAAAAATTCTGGAAATGGGTAGTGACA
GTAGTCAACATGATGAATGTACTTAATGACACTAAATTGTACACTTAAAAATGGTTAATA
CTGGGCTGGCGCAGTGGCTCATGGCTGTAAATCCCAGAACTTTGGGAGGCCAAGACAGGC
GGATCATGAGGTCAGGAGATTGAGACCATTCTGGCTAACATGGTGAAACCCTGTCTCTAC
TAAAAAATAAAAACAAATAAAAAAAAAAATTAGCCGGGCATGGTGGCAGGCACCTGTAGTC
CCAGCTACTCGGGAGGCTGAGGCAGGAGAATGGTGTGACCTGGGAGTCGGAGCTTGCAGT
GAGCTGAGATCGCGCCACTGCACTCCAGCCTGGGCAACAGAGCCAGATTCCGTCTCAAAA
AAAAAAAAAAAAAGGTTGATACCTGGGTGCGGTGGCTCATGCCTGTAATTTCAGCACTTT
GGGAGGCCAAGGCAGGCAGATCAGTTGAGGTCAAGAGTTAAGGACCAGCCTGGCCAACGT
GGCGAAACCCCATCTCTATTAAAAATACAAAAATTAGTCGAGTGTGGTGGTGGGTGCCTG
TAGTCCCAGCTGCTGGGAGGATGAGGCCTAGGAATTGCTTGAACCCAGGAGGCAGAGGTT
GCAGTGAGTTGAGATTGCGCCACTGCACTCCAGCCTGGGGGACAGAGCGAGACTTAGTCT
CAAAAAAAAGGTTAAAATTGTAAGTTTTGTTATGCATATTTTACCATAATCTTTAAAAAA
TAGATATATAGGAGATAAAGTCAACAGAATTTAATAACCAGTTGTAAATAGAGACTGAGT
GAGGAGGATGAATTAAGGAAGACATTGAGTACAACTTTTTGGTAGGTGAAAAACTCTTAA
AAAAATACGTGGGCAAAGATCCTACTTGATTCTTATAATTTAAAAATCTCCCAGTTAGTA
AACAAGGCTAGGTGGAGATTTGCATGTGATGTGAGGTGTGTGTTCTGTTTTGTAATGTGA
GGACTGTGAGCCATCTCCTGGACTTGAATATCCATTAGATAATTGAAAATACGGATTTGA
GAACTCAGGAGACGTGCAATGCAGTAACAAAACTCTGCACCTAGTTGATTTCTGTCTCCT
AATTTAATGCTTTTATGGGACAAACTGTTAGGCAGGTGGGCAAGATGGACAGCCATATTT
TTGTGGGTTTCTGGCCTGTGGGCCAGCCTCAGTGCTCACTCTGAGGTCATGTCCAAACTT
AGAACACATTCAGGCCTACCACAGTCAAGGCTCCCTTTCTCAACTCTAGTCCTCTGCACA
AATATCCGAAGCCTAGAAATAATAATCATCTGTCCTTGTGTCTTGCATTATGAAAGCCTA
GGAAAGGGCCTTGGGAATTAAGAAGAATGGAAAAACTGGTCTAACTGCTGCATGCTTCAG
CTTGCAGGGGAATCACTGAAATGGGGACAGGCCATAAAAGGACAACCAGAAGAGTGGCTT
CAGCAAAGGCATCGTTTTTCAGAGCAAGCTAGAGAATCCTGCCAGCGTCCTCAGGCAGGG
CCCCTGGGCACAGAGGTTAGGCAAGGGAGTGTCCCAGCATGTTGATGCCCTGAGCATCAG
AATAATGCCATAGAGGAGCTTCCAAAGAGTTCATTTCAGGTTTTGTAAGCCGAACATTTC
TAGGCAAATAAAATTTGATTTTGTGAATAAAGCTTGTTTCTTCAACTCCAGTGCAGATTC
TCATAGATTGATAGTGGCTTGTGATCCAGATAAAGAAAACAATTTTTCAAAGATTCATAT
TCTTTGTAGATGTACGGATTTAGAGACCATCTAATCTAACTCCCTCATTCTACAGATAGG
AAAAATGAGGCCTAAAGAAGTTAAGAAAATACCATGGAAATGTCACTGCTGAACTGCCAT
ACGTAGGATCCGAAAGAAATTGGGTAAATGCTACTGTGAGAAATACAGTACTAGGTCCAA
AGAATCTAATACAAATTAAAAATCTAAATGTTATTTCTAAAGCATCCCTGCACATGGCTG
AACTTACATAGTTTCATTTTCTTTCTTTTCTGTTGAAGAAGAGGCAATTGGCTGGGTGCA
GTGGCTCATGCCTGTAATCCTGGCACTTTGAGAGGCCGAGGCGGGTGGATCACCTGAGGT
CAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCCATCTCTACTAAAAATACAAA
AATTAGCTGGCTGTGGTGGCCGCTGCCTGTAATCCCAGCTACTCCAGAGGCTGAGGCAGG
AGAATTACTTGAATCTGGGAGGTGGAGGTTGCAGTGAGCCAAGATCACGCCATTGCACTC
TAGCCTGGATGACAAGAGGGAAACTCCATCTCAAAAAAAAAAAGAAAAAAAGCAATCACT
AACCTGTGTTGTTTATTAAACATGACAGACTGGCATGAAGTAATTACCAAACTGTAAACA

FIGURE 15.5

AAAAAGCTACAATCTGCCAGGCATGGTGGCTCATGCCTGTAATCCCCCACCTTGGGAGGC
CAGGTTGGGGGATCACCTGAGGCCTGGAGTTCAAGACTAGCCTGGTCAACATGGTGAAAC
CTCGTCTCTACTAAAAATACAAAAATTAGCCCGGCGTGGTGGCACATCCCTGTAATCCCA
GTTACTCAGGAGGCTGAGGCAGGAGAATCACTTGAACCTGGGCAGTGGGGAGGTTGCAGT
GAGCCAAGATCGCACCGTTGTACTCCAGTCTGGGCCGACAGAGTGAGACTCGGTCTCAAA
AAAAAGAAAAAAGAAAAGCTACAACCTTAATCTCAACTTCTCATAACATCATCTCTACTT
CTGATTAGAAGAGTGGAAGTGGGGAGGTTTATTACAAAAAGACTGTTATACCTTACACAC
TTCTCCCCATGAATAGTGAAGGTGTGAGTGAAAAAGACAGCAATTTTATTTTTTTTTTGA
AACAGGTTCTTGCACTGTCACCCGGGCTGGAGTGCACTGTTGTGATCACTGCTCACTGCA
GCCTCCACCTCCCAGGCTCAAGTGATCCTCCTACCTCAGCCTCCTGAGTAGCTGGGACCA
CAGTTGTGCACTACCATGCCCAGCTATTTTTTTTTTAAGAGATGGGGTCTCACTATATTGC
TTAGGCTAGTTCTCAAACTCCTGGCCTCAAGCAGTCCTCCGACCTTGGCCTCCCAAAGGG
TTGTGATTACAGGCATAAGCCACCACACCCAGCCAGCAGTTTTAGAATAAAGGGTGAAGG
TGCTGTTGGGGAAATATAATTTAAAAAACAAAATCTTCTCTCAACCCAGAAATCCTCTCC
ATGAAGGCAGTAGAGAAAGATAAGCTTTATTATTGAATAAAAATTAAATGAGAATGTGAT
GCACATCACAGGCACTTTGCTAAGAGATCACAAAGACAGAAGGAAATTTCACCATTTTGT
ACAGCCAAGCAGGTACAGCCCATTACATGTATGTTTTCGAGATAAATAGTCCTCAACTAA
GAGAACTTGACAGCACCACTGGTCACACAGTTCATTCTAACTTTACCTGATAATTGATGT
GACCACTTGTGTTATCTAAGATATCAACTTTTCGGGGGTGGGGGAGTGTGGAAACAGGAG
TTACTTTTATAGCTTGGTGCAAGGTACTCATTAAGATTAGGCTGTTACCCTCCCACAGAA
ACTGGAAGATAGGTATGCTATCTGGTAATGTTTACATTTCCCAGATCCTTGAGAAAGACA
TTCCTAGGTCATAAAGCTGACAAAAGGCTGATTCAGTTTTTAAATATATATATCTGTATA
TGTATTTCA

FIGURE 15.6

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actgagagacaggactagctggatttcctaggctgactaagaatccctaagcctagctgg
|||||||||||||||||||||||||||| |||| |||||||||| |||||||||||||||
actgagagacaggactagctggatttcccaggccgactaagaattcctaagcctagctgg

g-aaggtgaccacatccacctttaaacacggggcttgcaacttagctcacacctgaccaa
| |||||||||||| || ||||||||||| | ||||| |||| |||||||||| ||||||
ggaaggtgaccacaccctcctttaaacacagagcttgtaactcagctcacacccgaccaa

tcag---------agagctcactaaaatgctaattaggc-aaagacaggaggtaaagaaa
||||         ||||||||||||||| | |||||||| ||| ||||||||||||||||
tcaggtagtaaagagagctcactaaaataccaattaggctaaaaacaggaggtaaagaaa

tagccaa-tcatctattgcctgagagcacagcaggagggacaatgatcgggatataaacc
||  ||| |||||||| ||||||||||||||  |||||||||||||||||||||||||||
taatcaaatcatctatcgcctgagagcacagggggagggacaatgatcgggatataaacc

caagtcttcgagccggcaacggcaacccccttttgggtcccctccctttgtatgggagctc
|| |  || ||||| |    || ||||| |||||||||||||| |  |||||||||||||
caggcatttgagccagatcaggtaaccctctttgggtcccctcacactgtatgggagctc

tgttttcatgctatttcactctattaaatcttgcaactgcac--tcttctggtccatgtt
||||          ||||||||||||||||||||||||||||  ||||||||||||||||
tgtt----------ttcactctattaaatcttgcaactgcacactcttctggtccatgtt

tcttacggcttgagctgagctttcgctcgccatccaccactgctgtttgccgccaccgca
| || |||||  ||||||||||| ||||||| |||||||||||||  ||||||||  |||
tgttccggctcaagctgagcttttgctcgccgtccaccactgctgaatgccgccattgca

gacccgccgctgactcccatccctctggatcatgcagggtgtccgctgtgctcctgatcc
|||| |||  ||||| ||| ||||| |||||  |||| ||||||||||  ||||||||||
gacctgcccttgacttccacccctccggatccggcagagtgtccgctgcactcctgatcc

agcgaggcacccattgccgctcccaatcgggctaaaggcttgccattgttcctgcatggc
|||||||||||||||||| ||||| ||| |||||||||||||||||||||||||||  ||
agcgaggcacccattgccactcccgatcaggctaaaggcttgccattgttcctgcacagc

taagtgcctgggttcatcctaattgagctgaacactagtcactgggttccatggttctct
|||||||||||||||||||||||   |||||||||| ||| |||||||||| ||||||||
taagtgcctgggttcatcctaatcaggctgaacactggtcgctgggttccacggttctct

tctgtgacccacagcttctaatagagctataacactcaccgcatggcccaaggttccatt
||  |||| ||||||||||||||||||||||||||||||| |||||||||||||||||||
tccatgactcacagcttctaatagagctataacactcaccacatggcccaaggttccatt

cctt-gaatccataaggccaagaaccccaggtcagagaacacgaggcttgccaccatctt
| || |||||||| ||||||||||||||||||||||||| |  ||||  ||| |||||||
cgttggaatccatgaggccaagaaccccaggtcagagaataaaaggcccgcc-ccatctt

gggag
|||||
gggag
```

FIGURE 16

TCCTGTGAAC CTCTAGAGGA TTTGCGCCTG CTCTTCAAAC AACAACCAGG AGGAAAGTAA 7860

CTAAAATCAT AAATCCCCAT GGCCCTCCCT TATCATATTT TTCTCTTTAC TGTTCTTTTA 7920

CCCTCTTTCA CTCTCACTGC ACCCCCTCCA TGCCGCTGTA TGACCAGTAG CTCCCCTTAC 7980

CAAGAGTTTC TATGGAGAAT GCAGCGTCCC GGAAATATTG ATGCCCCATC GTATAGGAGT 8040

CTTTCTAAGG GAACCCCCAC CTTCACTGCC CACACCCATA TGCCCCGCAA CTGCTATCAC 8100

TCTGCCACTC TTTGCATGCA TGCAAATACT CATTATTGGA CAGGAAAAAT GATTAATCCT 8160

AGTTGTCCTG GAGGACTTGG AGTCACTGTC TGTTGGACTT ACTTCACCCA AACTGGTATG 8220

TCTGATGGGG GTGGAGTTCA AGATCAGGCA AGAGAAAAAC ATGTAAAAGA AGTAATCTCC 8280

CAACTCACCC GGGTACATGG CACCTCTAGC CCCTACAAAG GACTAGATCT CTCAAAACTA 8340

CATGAAACCC TCCGTACCCA TACTCGCCTG GTAAGCCTAT TTAATACCAC CCTCACTGGG 8400

CTCCATGAGG TCTCGGCCCA AAACCCTACT AACTGTTGGA TATGCCTCCC CCTGAACTTC 8460

AGGCCATATG TTTCAATCCC TGTACCTGAA CAATGGAACA ACTTCAGCAC AGAAATAAAC 8520

ACCACTTCCG TTTTAGTAGG ACCTCTTGTT TCCAATCTGG AAATAACCCA TACCTCAAAC 8580

CTCACCTGTG TAAAATTTAG CAATACTACA TACACAACCA ACTCCCAATG CATCAGGTGG 8640

GTAACTCCTC CCACACAAAT AGTCTGCCTA CCCTCAGGAA TATTTTTTGT CTGTGGTACC 8700

TCAGCCTATC GTTGTTTGAA TGGCTCTTCA GAATCTATGT GCTTCCTCTC ATTCTTAGTG 8760

CCCCCTATGA CCATCTACAC TGAACAAGAT TTATACAGTT ATGTCATATC TAAGCCCCGC 8820

AACAAAAGAG TACCCATTCT TCCTTTTGTT ATAGGAGCAG GAGTGCTAGG TGCACTAGGT 8880

ACTGGCATTG GCGGTATCAC AACCTCTACT CAGTTCTACT ACAAACTATC TCAAGAACTA 8940

AATGGGGACA TGGAACGGGT CGCCGACTCC CTGGTCACCT TGCAAGATCA ACTTAACTCC 9000

CTAGCAGCAG TAGTCCTTCA AAATCGAAGA GCTTTAGACT TGCTAACCGC TGAAAGAGGG 9060

GGAACCTGTT TATTTTTAGG GGAAGAATGC TGTTATTATG TTAATCAATC CGGAATCGTC 9120

ACTGAGAAAG TTAAAGAAAT TCGAGATCGA ATACAACGTA GAGCAGAGGA GCTTCGAAAC 9180

ACTGGACCCT GGGGCCTCCT CAGCCAATGG ATGCCCTGGA TTCTCCCCTT CTTAGGACCT 9240

CTAGCAGCTA TAATATTGCT ACTCCTCTTT GGACCCTGTA TCTTTAACCT CCTTGTTAAC 9300

TTTGTCTCTT CCAGAATCGA AGCTGTAAAA CTACAAATGG AGCCCAAGAT GCAGTCCAAG 9360

ACTAAGATCT ACCGCAGACC CCTGGACCGG CCTGCTAGCC CACGATCTGA TGTTAATGAC 9420

ATCAAAGGCA CCCCTCCTGA GGAAATCTCA GCTGCACAAC CTCTACTACG CCCCAATTCA 9480

GCAGGAAGCA GT**TAG**AGCGG *TCTCGGCCAA CCTCCCCAAC* AGCACTTAGG TTTTCCTGTT 9540

FIGURE 17

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AAGCTCCTTCAGGAGAACAAAGAACAGGCCATTACCCTGGAGAAGACTGGCAACTGATTTTACCCACAAGCCCAA
LysLeuLeuGlnGluAsnLysGluGlnAlaIleThrLeuGluLysThrGlyAsn...PheTyrProGlnAlaGln
  SerSerPheArgArgThrLysAsnArgProLeuProTrpArgArgLeuAlaThrAspPheThrHisLysProLys
   AlaProSerGlyGluGlnArgThrGlyHisTyrProGlyGluAspTrpGlnLeuIleLeuProThrSerProAsn

ACCTCAGGGATTTCAGTATCTACTAGTCTGGGTAGATACTTTCACGGGTTGGGCAGAGGCCTTCCCCTGTAGGAC
ThrSerGlyIleSerValSerThrSerLeuGlyArgTyrPheHisGlyLeuGlyArgGlyLeuProLeu...Asp
  ProGlnGlyPheGlnTyrLeuLeuValTrpValAspThrPheThrGlyTrpAlaGluAlaPheProCysArgThr
   LeuArgAspPheSerIleTyr...SerGly...IleLeuSerArgValGlyGlnArgProSerProValGlyGln

AGAAAAGGCCCAAGAGGTAATAAAGGCACTAGTTCATGAAATAATTCCCAGATTCGGACTTCCCCGAGGCTTACA
ArgLysGlyProArgGlyAsnLysGlyThrSerSer...AsnAsnSerGlnIleArgThrSerProArgLeuThr
  GluLysAlaGlnGluValIleLysAlaLeuValHisGluIleIleProArgPheGlyLeuProArgGlyLeuGln
   LysArgProLysArg......ArgHis...PheMETLys...PheProAspSerAspPheProGluAlaTyrArg

GAGTGACAATAGCCCTGCTTTCCAGGCCACAGTAACCCAGGGAGTATCCCAGGCGTTAGGTATACGATATCACTT
Glu...Gln...ProCysPheProGlyHisSerAsnProGlySerIleProGlyValArgTyrThrIleSerLeu
  SerAspAsnSerProAlaPheGlnAlaThrValThrGlnGlyValSerGlnAlaLeuGlyIleArgTyrHisLeu
   ValThrIleAlaLeuLeuSerArgProGln...ProArgGluTyrProArgArg...ValTyrAspIleThrTyr

ACACTGCGCCTGAAGGCCACAGTCCTCAGGGAAGGTCGAGAAAATGAATGAAACACTCAAAGGACATCTAAAAAA
ThrLeuArgLeuLysAlaThrValLeuArgGluGlyArgGluAsnGlu...AsnThrGlnArgThrSerLysLys
  HisCysAla...ArgProGlnSerSerGlyLysValGluLysMETAsnGluThrLeuLysGlyHisLeuLysLys
   ThrAlaProGluGlyHisSerProGlnGlyArgSerArgLys...METLysHisSerLysAspIle...LysSer

GCAAACCCAGGAAACCCACCTCACATGGCCTGCTCTGTTGCCTATAGCCTTAAAAAGAATCTGCAACTTTCCCCA
           385       395       405       415       425       435       445
AlaAsnProGlyAsnProProHisMETAlaCysSerValAlaTyrSerLeuLysLysAsnLeuGlnLeuSerPro
  GlnThrGlnGluThrHisLeuThrTrpProAlaLeuLeuProIleAlaLeuLysArgIleCysAsnPheProGln
   LysProArgLysProThrSerHisGlyLeuLeuCysCysLeu...Pro...LysGluSerAlaThrPheProLys

AAAAGCAGGACTTAGCCCATACGAAATGCTGTATGGAAGGCCCTTCATAACCAATGACCTTGTGCTTGACCCAAG
LysSerArgThr...ProIleArgAsnAlaValTrpLysAlaLeuHisAsnGln...ProCysAla...ProLys
  LysAlaGlyLeuSerProTyrGluMETLeuTyrGlyArgProPheIleThrAsnAspLeuValLeuAspProArg
   LysGlnAspLeuAlaHisThrLysCysCysMETGluGlyProSer...ProMETThrLeuCysLeuThrGlnAsp

ACAGCCAACTTAGTTGCAGACATCACCTCCTTAGCCAAATATCAACAAGTTCTTAAAACATTACAAGGAACCTAT
ThrAlaAsnLeuValAlaAspIleThrSerLeuAlaLysTyrGlnGlnValLeuLysThrLeuGlnGlyThrTyr
  GlnProThr...LeuGlnThrSerProPro...ProAsnIleAsnLysPheLeuLysHisTyrLysGluProIle
   SerGlnLeuSerCysArgHisHisLeuLeuSerGlnIleSerThrSerSer...AsnIleThrArgAsnLeuSer

CCCTGAGAAGAGGGAAAAGAACTATTCCACCCTTGTGACATGGTATTAGTCAAGTCCCTTCCCTCTAATTCCCCA
Pro...GluGluGlyLysGluLeuPheHisProCysAspMETValLeuValLysSerLeuProSerAsnSerPro
  ProGluLysArgGluLysAsnTyrSerThrLeuValThrTrpTyr...SerSerProPheProLeuIleProHis
   LeuArgArgGlyLysArgThrIleProProLeu...HisGlyIleSerGlnValProSerLeu...PheProIle

TCCCTAGATACATCCTGGGAAGGACCCTACCCAGTCATTTTATCTACCCCAACTGCGGTTAAAGTGGCTGGAGTG
SerLeuAspThrSerTrpGluGlyProTyrProValIleLeuSerThrProThrAlaValLysValAlaGlyVal
  Pro...IleHisProGlyLysAspProThrGlnSerPheTyrLeuProGlnLeuArgLeuLysTrpLeuGluTrp
   ProArgTyrIleLeuGlyArgThrLeuProSerHisPheIleTyrProAsnCysGly...SerGlyTrpSerGly
```

FIGURE 18.1

GAGTCTTGGATACATCACACTTGAGTCAAATCCTGGATACTGCCAAAGGAACCTGAAAATCCAGGAGACAACGCT
GluSerTrpIleHisHisThr...ValLysSerTrpIleLeuProLysGluProGluAsnProGlyAspAsnAla
SerLeuGlyTyrIleThrLeuGluSerAsnProGlyTyrCysGlnArgAsnLeuLysIleGlnGluThrThrLeu
ValLeuAspThrSerHisLeuSerGlnIleLeuAspThrAlaLysGlyThr...LysSerArgArgGlnArg...

AGCTATTCCTGTGAACCTCTAGAGGATTTGCGCCTGCTCTTCAAACAACAACCAGGAGGAAAGTAACTAAAATCA
SerTyrSerCysGluProLeuGluAspLeuArgLeuLeuPheLysGlnGlnProGlyGlyLys...LeuLysSer
AlaIleProValAsnLeu...ArgIleCysAlaCysSerSerAsnAsnAsnGlnGluGluSerAsn...AsnHis
LeuPheLeu...ThrSerArgGlyPheAlaProAlaLeuGlnThrThrThrArgArgLysValThrLysIleIle

TAAATCCCCATGGCCCTCCCTTATCATATTTTTCTCTTTACTGTTCTTTTACCCTCTTTCACTCTCACTGCACCC
...IleProMETAlaLeuProTyrHisIlePheLeuPheThrValLeuLeuProSerPheThrLeuThrAlaPro
LysSerProTrpProSerLeuIleIlePhePheSerLeuLeuPhePheTyrProLeuSerLeuSerLeuHisPro
AsnProHisGlyProProLeuSerTyrPheSerLeuTyrCysSerPheThrLeuPheHisSerHisCysThrPro

CCTCCATGCCGCTGTATGACCAGTAGCTCCCCTTACCAAGAGTTTCTATGGAGAATGCAGCGTCCCGGAAATATT
ProProCysArgCysMETThrSerSerSerProTyrGlnGluPheLeuTrpArgMETGlnArgProGlyAsnIle
LeuHisAlaAlaVal...ProValAlaProLeuThrLysSerPheTyrGlyGluCysSerValProGluIleLeu
SerMETProLeuTyrAspGln...LeuProLeuProArgValSerMETGluAsnAlaAlaSerArgLysTyr...

GATGCCCCATCGTATAGGAGTCTTTCTAAGGGAACCCCCACCTTCACTGCCCACACCCATATGCCCCGCAACTGC
AspAlaProSerTyrArgSerLeuSerLysGlyThrProThrPheThrAlaHisThrHisMETProArgAsnCys
METProHisArgIleGlyValPheLeuArgGluProProProSerLeuProThrProIleCysProAlaThrAla
CysProIleVal...GluSerPhe...GlyAsnProHisLeuHisCysProHisProTyrAlaProGlnLeuLeu

TATCACTCTGCCACTCTTTGCATGCATGCAAATACTCATTATTGGACAGGAAAAATGATTAATCCTAGTTGTCCT
TyrHisSerAlaThrLeuCysMETHisAlaAsnThrHisTyrTrpThrGlyLysMETIleAsnProSerCysPro
IleThrLeuProLeuPheAlaCysMETGlnIleLeuIleIleGlyGlnGluLys...LeuIleLeuValValLeu
SerLeuCysHisSerLeuHisAlaCysLysTyrSerLeuLeuAspArgLysAsnAsp...Ser...LeuSerTrp

GGAGGACTTGGAGTCACTGTCTGTTGGACTTACTTCACCCAAACTGGTATGTCTGATGGGGGTGGAGTTCAAGAT
GlyGlyLeuGlyValThrValCysTrpThrTyrPheThrGlnThrGlyMETSerAspGlyGlyGlyValGlnAsp
GluAspLeuGluSerLeuSerValGlyLeuThrSerProLysLeuValCysLeuMETGlyValGluPheLysIle
ArgThrTrpSerHisCysLeuLeuAspLeuLeuHisProAsnTrpTyrVal...TrpGlyTrpSerSerArgSer

CAGGCAAGAGAAAAACATGTAAAAGAAGTAATCTCCCAACTCACCCGGGTACATGGCACCTCTAGCCCCTACAAA
GlnAlaArgGluLysHisValLysGluValIleSerGlnLeuThrArgValHisGlyThrSerSerProTyrLys
ArgGlnGluLysAsnMET...LysLys...SerProAsnSerProGlyTyrMETAlaProLeuAlaProThrLys
GlyLysArgLysThrCysLysArgSerAsnLeuProThrHisProGlyThrTrpHisLeu...ProLeuGlnArg

GGACTAGATCTCTCAAAACTACATGAAACCCTCCGTACCCATACTCGCCTGGTAAGCCTATTTAATACCACCCTC
GlyLeuAspLeuSerLysLeuHisGluThrLeuArgThrHisThrArgLeuValSerLeuPheAsnThrThrLeu
Asp...IleSerGlnAsnTyrMETLysProSerValProIleLeuAlaTrp...AlaTyrLeuIleProProSer
ThrArgSerLeuLysThrThr...AsnProProTyrProTyrSerProGlyLysProIle...TyrHisProHis

ACTGGGCTCCATGAGGTCTCGGCCCAAAACCCTACTAACTGTTGGATATGCCTCCCCCTGAACTTCAGGCCATAT
ThrGlyLeuHisGluValSerAlaGlnAsnProThrAsnCysTrpIleCysLeuProLeuAsnPheArgProTyr
LeuGlySerMETArgSerArgProLysThrLeuLeuThrValGlyTyrAlaSerPro...ThrSerGlyHisMET
TrpAlaPro...GlyLeuGlyProLysProTyr...LeuLeuAspMETProProProGluLeuGlnAlaIleCys

GTTTCAATCCCTGTACCTGAACAATGGAACAACTTCAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCT
ValSerIleProValProGluGlnTrpAsnAsnPheSerThrGluIleAsnThrThrSerValLeuValGlyPro
PheGlnSerLeuTyrLeuAsnAsnGlyThrThrSerAlaGlnLys...ThrProLeuProPhe......AspLeu
PheAsnProCysThr...ThrMETGluGlnLeuGlnHisArgAsnLysHisHisPheArgPheSerArgThrSer

FIGURE 18.2

CTTGTTTCCAATCTGGAAATAACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTACATACACAACC
LeuValSerAsnLeuGluIleThrHisThrSerAsnLeuThrCysValLysPheSerAsnThrThrTyrThrThr
LeuPheProIleTrpLys...ProIleProGlnThrSerProVal...AsnLeuAlaIleLeuHisThrGlnPro
CysPheGlnSerGlyAsnAsnProTyrLeuLysProHisLeuCysLysIle...GlnTyrTyrIleHisAsnGln

AACTCCCAATGCATCAGGTGGGTAACTCCTCCCACACAAATAGTCTGCCTACCCTCAGGAATATTTTTTGTCTGT
AsnSerGlnCysIleArgTrpValThrProProThrGlnIleValCysLeuProSerGlyIlePhePheValCys
ThrProAsnAlaSerGlyGly...LeuLeuProHisLys...SerAlaTyrProGlnGluTyrPheLeuSerVal
LeuProMETHisGlnValGlyAsnSerSerHisThrAsnSerLeuProThrLeuArgAsnIlePheCysLeuTrp

GGTACCTCAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCATTCTTAGTGCCCCCTATG
GlyThrSerAlaTyrArgCysLeuAsnGlySerSerGluSerMETCysPheLeuSerPheLeuValProProMET
ValProGlnProIleValVal...METAlaLeuGlnAsnLeuCysAlaSerSerHisSer...CysProLeu...
TyrLeuSerLeuSerLeuPheGluTrpLeuPheArgIleTyrValLeuProLeuIleLeuSerAlaProTyrAsp

ACCATCTACACTGAACAAGATTTATACAGTTATGTCATATCTAAGCCCCGCAACAAAAGAGTACCCATTCTTCCT
ThrIleTyrThrGluGlnAspLeuTyrSerTyrValIleSerLysProArgAsnLysArgValProIleLeuPro
ProSerThrLeuAsnLysIleTyrThrValMETSerTyrLeuSerProAlaThrLysGluTyrProPhePheLeu
HisLeuHis...ThrArgPheIleGlnLeuCysHisIle...AlaProGlnGlnLysSerThrHisSerSerPhe

TTTGTTATAGGAGCAGGAGTGCTAGGTGCACTAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTAC
PheValIleGlyAlaGlyValLeuGlyAlaLeuGlyThrGlyIleGlyGlyIleThrThrSerThrGlnPheTyr
LeuLeu...GluGlnGluCys...ValHis...ValLeuAlaLeuAlaValSerGlnProLeuLeuSerSerThr
CysTyrArgSerArgSerAlaArgCysThrArgTyrTrpHisTrpArgTyrHisAsnLeuTyrSerValLeuLeu

TACAAACTATCTCAAGAACTAAATGGGGACATGGAACGGGTCGCCGACTCCCTGGTCACCTTGCAAGATCAACTT
TyrLysLeuSerGlnGluLeuAsnGlyAspMETGluArgValAlaAspSerLeuValThrLeuGlnAspGlnLeu
ThrAsnTyrLeuLysAsn...METGlyThrTrpAsnGlySerProThrProTrpSerProCysLysIleAsnLeu
GlnThrIleSerArgThrLysTrpGlyHisGlyThrGlyArgArgLeuProGlyHisLeuAlaArgSerThr...

AACTCCCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGGGAACCTGT
AsnSerLeuAlaAlaValValLeuGlnAsnArgArgAlaLeuAspLeuLeuThrAlaGluArgGlyGlyThrCys
ThrPro...GlnGln...SerPheLysIleGluGluLeu...ThrCys...ProLeuLysGluGlyGluProVal
LeuProSerSerSerSerProSerLysSerLysSerPheArgLeuAlaAsnArg...LysArgGlyAsnLeuPhe

TTATTTTTAGGGGAAGAATGCTGTTATTATGTTAATCAATCCGGAATCGTCACTGAGAAAGTTAAAGAAATTCGA
LeuPheLeuGlyGluGluCysCysTyrTyrValAsnGlnSerGlyIleValThrGluLysValLysGluIleArg
TyrPhe...GlyLysAsnAlaValIleMETLeuIleAsnProGluSerSerLeuArgLysLeuLysLysPheGlu
IlePheArgGlyArgMETLeuLeuLeuCys...SerIleArgAsnArgHis...GluSer...ArgAsnSerArg

GATCGAATACAACGTAGAGCAGAGGAGCTTCGAAACACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCTGG
AspArgIleGlnArgArgAlaGluGluLeuArgAsnThrGlyProTrpGlyLeuLeuSerGlnTrpMETProTrp
IleGluTyrAsnValGluGlnArgSerPheGluThrLeuAspProGlyAlaSerSerAlaAsnGlyCysProGly
SerAsnThrThr...SerArgGlyAlaSerLysHisTrpThrLeuGlyProProGlnProMETAspAlaLeuAsp

ATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTCTTTGGACCCTGTATCTTTAACCTCCTT
IleLeuProPheLeuGlyProLeuAlaAlaIleIleLeuLeuLeuLeuPheGlyProCysIlePheAsnLeuLeu
PheSerProSer...AspLeu...GlnLeu...TyrCysTyrSerSerLeuAspProValSerLeuThrSerLeu
SerProLeuLeuArgThrSerSerSerTyrAsnIleAlaThrProLeuTrpThrLeuTyrLeu...ProProCys

FIGURE 18.3

GTTAACTTTGTCTCTTCCAGAATCGAAGCTGTAAAACTACAAATGGAGCCCAAGATGCAGTCCAAGACTAAGATC
ValAsnPheValSerSerArgIleGluAlaValLysLeuGlnMETGluProLysMETGlnSerLysThrLysIle
LeuThrLeuSerLeuProGluSerLysLeu...AsnTyrLysTrpSerProArgCysSerProArgLeuArgSer
...LeuCysLeuPheGlnAsnArgSerCysLysThrThrAsnGlyAlaGlnAspAlaValGlnAsp...AspLeu

TACCGCAGACCCCTGGACCGGCCTGCTAGCCCACGATCTGATGTTAATGACATCAAAGGCACCCCTCCTGAGGAA
TyrArgArgProLeuAspArgProAlaSerProArgSerAspValAsnAspIleLysGlyThrProProGluGlu
ThrAlaAspProTrpThrGlyLeuLeuAlaHisAspLeuMETLeuMETThrSerLysAlaProLeuLeuArgLys
ProGlnThrProGlyProAlaCys...ProThrIle...Cys......HisGlnArgHisProSer...GlyAsn

ATCTCAGCTGCACAACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCCCCA
IleSerAlaAlaGlnProLeuLeuArgProAsnSerAlaGlySerSer...SerGlyArgArgProThrSerPro
SerGlnLeuHisAsnLeuTyrTyrAlaProIleGlnGlnGluAlaValArgAlaValValGlyGlnProProGln
LeuSerCysThrThrSerThrThrProGlnPheSerArgLysGlnLeuGluArgSerSerAlaAsnLeuProAsn

ACAGCACTTAGGTTTTCCTGTTGAGATGGGGG
ThrAlaLeuArgPheSerCys...AspGlyGly
GlnHisLeuGlyPheProValGluMETGly
SerThr...ValPheLeuLeuArgTrpGly

FIGURE 18.4

LysLeuLeuGlnGluAsnLysGluGlnAlaIleThrLeuGluLysThrGlyAsn...PheTyrProGlnAlaGln
ThrSerGlyIleSerValSerThrSerLeuGlyArgTyrPheHisGlyLeuGlyArgGlyLeuProLeu...Asp
ArgLysGlyProArgGlyAsnLysGlyThrSerSer...AsnAsnSerGlnIleArgThrSerProArgLeuThr
Glu...Gln...ProCysPheProGlyHisSerAsnProGlySerIleProGlyValArgTyrThrIleSerLeu
ThrLeuArgLeuLysAlaThrValLeuArgGluGlyArgGluAsnGlu...AsnThrGlnArgThrSerLysLys

AlaAsnProGlyAsnProProHisMETAlaCysSerValAlaTyrSerLeuLysLysAsnLeuGlnLeuSerPro
LysSerArgThr...ProIleArgAsnAlaValTrpLysAlaLeuHisAsnGln...ProCysAla...ProLys
ThrAlaAsnLeuValAlaAspIleThrSerLeuAlaLysTyrGlnGlnValLeuLysThrLeuGlnGlyThrTyr
Pro...GluGluGlyLysGluLeuPheHisProCysAspMETValLeuValLysSerLeuProSerAsnSerPro
SerLeuAspThrSerTrpGluGlyProTyrProValIleLeuSerThrProThrAlaValLysValAlaGlyVal
GluSerTrpIleHisHisThr...ValLysSerTrpIleLeuProLysGluProGluAsnProGlyAspAsnAla
SerTyrSerCysGluProLeuGluAspLeuArgLeuLeuPheLysGlnGlnProGlyGlyLys...LeuLysSer
...IleProMETAlaLeuProTyrHisIlePheLeuPheThrValLeuLeuProSerPheThrLeuThrAlaPro
ProProCysArgCysMETThrSerSerSerProTyrGlnGluPheLeuTrpArgMETGlnArgProGlyAsnIle
AspAlaProSerTyrArgSerLeuSerLysGlyThrProThrPheThrAlaHisThrHisMETProArgAsnCys
TyrHisSerAlaThrLeuCysMETHisAlaAsnThrHisTyrTrpThrGlyLysMETIleAsnProSerCysPro
GlyGlyLeuGlyValThrValCysTrpThrTyrPheThrGlnThrGlyMETSerAspGlyGlyGlyValGlnAsp
GlnAlaArgGluLysHisValLysGluValIleSerGlnLeuThrArgValHisGlyThrSerSerProTyrLys
GlyLeuAspLeuSerLysLeuHisGluThrLeuArgThrHisThrArgLeuValSerLeuPheAsnThrThrLeu
ThrGlyLeuHisGluValSerAlaGlnAsnProThrAsnCysTrpIleCysLeuProLeuAsnPheArgProTyr
ValSerIleProValProGluGlnTrpAsnAsnPheSerThrGluIleAsnThrThrSerValLeuValGlyPro
LeuValSerAsnLeuGluIleThrHisThrSerAsnLeuThrCysValLysPheSerAsnThrThrTyrThrThr
AsnSerGlnCysIleArgTrpValThrProProThrGlnIleValCysLeuProSerGlyIlePhePheValCys
GlyThrSerAlaTyrArgCysLeuAsnGlySerSerGluSerMETCysPheLeuSerPheLeuValProProMET
ThrIleTyrThrGluGlnAspLeuTyrSerTyrValIleSerLysProArgAsnLysArgValProIleLeuPro
PheValIleGlyAlaGlyValLeuGlyAlaLeuGlyThrGlyIleGlyGlyIleThrThrSerThrGlnPheTyr
TyrLysLeuSerGlnGluLeuAsnGlyAspMETGluArgValAlaAspSerLeuValThrLeuGlnAspGlnLeu

FIGURE 19.1

AsnSerLeuAlaAlaValValLeuGlnAsnArgArgAlaLeuAspLeuLeuThrAlaGluArgGlyGlyThrCys

LeuPheLeuGlyGluGluCysCysTyrTyrValAsnGlnSerGlyIleValThrGluLysValLysGluIleArg

AspArgIleGlnArgArgAlaGluGluLeuArgAsnThrGlyProTrpGlyLeuLeuSerGlnTrpMETProTrp

IleLeuProPheLeuGlyProLeuAlaAlaIleIleLeuLeuLeuLeuPheGlyProCysIlePheAsnLeuLeu

ValAsnPheValSerSerArgIleGluAlaValLysLeuGlnMETGluProLysMETGlnSerLysThrLysIle

TyrArgArgProLeuAspArgProAlaSerProArgSerAspValAsnAspIleLysGlyThrProProGluGlu

IleSerAlaAlaGlnProLeuLeuArgProAsnSerAlaGlySerSer...SerGlyArgArgProThrSerPro

ThrAlaLeuArgPheSerCys...AspGlyGly

FIGURE 19.2

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SerSerPheArgArgThrLysAsnArgProLeuProTrpArgArgLeuAlaThrAspPheThrHisLysProLys
ProGlnGlyPheGlnTyrLeuLeuValTrpValAspThrPheThrGlyTrpAlaGluAlaPheProCysArgThr
GluLysAlaGlnGluValIleLysAlaLeuValHisGluIleIleProArgPheGlyLeuProArgGlyLeuGln
SerAspAsnSerProAlaPheGlnAlaThrValThrGlnGlyValSerGlnAlaLeuGlyIleArgTyrHisLeu
HisCysAla...ArgProGlnSerSerGlyLysValGluLysMETAsnGluThrLeuLysGlyHisLeuLysLys
GlnThrGlnGluThrHisLeuThrTrpProAlaLeuLeuProIleAlaLeuLysArgIleCysAsnPheProGln
LysAlaGlyLeuSerProTyrGluMETLeuTyrGlyArgProPheIleThrAsnAspLeuValLeuAspProArg
GlnProThr...LeuGlnThrSerProPro...ProAsnIleAsnLysPheLeuLysHisTyrLysGluProIle
ProGluLysArgGluLysAsnTyrSerThrLeuValThrTrpTyr...SerSerProPheProLeuIleProHis
Pro...IleHisProGlyLysAspProThrGlnSerPheTyrLeuProGlnLeuArgLeuLysTrpLeuGluTrp
SerLeuGlyTyrIleThrLeuGluSerAsnProGlyTyrCysGlnArgAsnLeuLysIleGlnGluThrThrLeu
AlaIleProValAsnLeu...ArgIleCysAlaCysSerSerAsnAsnAsnGlnGluGluSerAsn...AsnHis
LysSerProTrpProSerLeuIleIlePhePheSerLeuLeuPhePheTyrProLeuSerLeuSerLeuHisPro
LeuHisAlaAlaVal...ProValAlaProLeuThrLysSerPheTyrGlyGluCysSerValProGluIleLeu
METProHisArgIleGlyValPheLeuArgGluProProProSerLeuProThrProIleCysProAlaThrAla
IleThrLeuProLeuPheAlaCysMETGlnIleLeuIleIleGlyGlnGluLys...LeuIleLeuValValLeu
GluAspLeuGluSerLeuSerValGlyLeuThrSerProLysLeuValCysLeuMETGlyValGluPheLysIle
ArgGlnGluLysAsnMET...LysLys...SerProAsnSerProGlyTyrMETAlaProLeuAlaProThrLys
Asp...IleSerGlnAsnTyrMETLysProSerValProIleLeuAlaTrp...AlaTyrLeuIleProProSer
LeuGlySerMETArgSerArgProLysThrLeuLeuThrValGlyTyrAlaSerPro...ThrSerGlyHisMET
PheGlnSerLeuTyrLeuAsnAsnGlyThrThrSerAlaGlnLys...ThrProLeuProPhe......AspLeu
LeuPheProIleTrpLys...ProIleProGlnThrSerProVal...AsnLeuAlaIleLeuHisThrGlnPro
ThrProAsnAlaSerGlyGly...LeuLeuProHisLys...SerAlaTyrProGlnGluTyrPheLeuSerVal
ValProGlnProIleValVal...METAlaLeuGlnAsnLeuCysAlaSerSerHisSer...CysProLeu...
ProSerThrLeuAsnLysIleTyrThrValMETSerTyrLeuSerProAlaThrLysGluTyrProPhePheLeu
LeuLeu...GluGlnGluCys...ValHis...ValLeuAlaLeuAlaValSerGlnProLeuLeuSerSerThr
ThrAsnTyrLeuLysAsn...METGlyThrTrpAsnGlySerProThrProTrpSerProCysLysIleAsnLeu
ThrPro...GlnGln...SerPheLysIleGluGluLeu...ThrCys...ProLeuLysGluGlyGluProVal

FIGURE 20.1

TyrPhe...GlyLysAsnAlaValIleMETLeuIleAsnProGluSerSerLeuArgLysLeuLysLysPheGlu

IleGluTyrAsnValGluGlnArgSerPheGluThrLeuAspProGlyAlaSerSerAlaAsnGlyCysProGly

PheSerProSer...AspLeu...GlnLeu...TyrCysTyrSerSerLeuAspProValSerLeuThrSerLeu

LeuThrLeuSerLeuProGluSerLysLeu...AsnTyrLysTrpSerProArgCysSerProArgLeuArgSer

ThrAlaAspProTrpThrGlyLeuLeuAlaHisAspLeuMETLeuMETThrSerLysAlaProLeuLeuArgLys

SerGlnLeuHisAsnLeuTyrTyrAlaProIleGlnGlnGluAlaValArgAlaValValGlyGlnProProGln

GlnHisLeuGlyPheProValGluMETGly

FIGURE 20.2

AlaProSerGlyGluGlnArgThrGlyHisTyrProGlyGluAspTrpGlnLeuIleLeuProThrSerProAsn
LeuArgAspPheSerIleTyr...SerGly...IleLeuSerArgValGlyGlnArgProSerProValGlyGln
LysArgProLysArg......ArgHis...PheMETLys...PheProAspSerAspPheProGluAlaTyrArg
ValThrIleAlaLeuLeuSerArgProGln...ProArgGluTyrProArgArg...ValTyrAspIleThrTyr
ThrAlaProGluGlyHisSerProGlnGlyArgSerArgLys...METLysHisSerLysAspIle...LysSer
LysProArgLysProThrSerHisGlyLeuLeuCysCysLeu...Pro...LysGluSerAlaThrPheProLys
LysGlnAspLeuAlaHisThrLysCysCysMETGluGlyProSer...ProMETThrLeuCysLeuThrGlnAsp
SerGlnLeuSerCysArgHisHisLeuLeuSerGlnIleSerThrSerSer...AsnIleThrArgAsnLeuSer
LeuArgArgGlyLysArgThrIleProProLeu...HisGlyIleSerGlnValProSerLeu...PheProIle
ProArgTyrIleLeuGlyArgThrLeuProSerHisPheIleTyrProAsnCysGly...SerGlyTrpSerGly
ValLeuAspThrSerHisLeuSerGlnIleLeuAspThrAlaLysGlyThr...LysSerArgArgGlnArg...
LeuPheLeu...ThrSerArgGlyPheAlaProAlaLeuGlnThrThrThrArgArgLysValThrLysIleIle
AsnProHisGlyProProLeuSerTyrPheSerLeuTyrCysSerPheThrLeuPheHisSerHisCysThrPro
SerMETProLeuTyrAspGln...LeuProLeuProArgValSerMETGluAsnAlaAlaSerArgLysTyr...
CysProIleVal...GluSerPhe...GlyAsnProHisLeuHisCysProHisProTyrAlaProGlnLeuLeu
SerLeuCysHisSerLeuHisAlaCysLysTyrSerLeuLeuAspArgLysAsnAsp...Ser...LeuSerTrp
ArgThrTrpSerHisCysLeuLeuAspLeuLeuHisProAsnTrpTyrVal...TrpGlyTrpSerSerArgSer
GlyLysArgLysThrCysLysArgSerAsnLeuProThrHisProGlyThrTrpHisLeu...ProLeuGlnArg
ThrArgSerLeuLysThrThr...AsnProProTyrProTyrSerProGlyLysProIle...TyrHisProHis
TrpAlaPro...GlyLeuGlyProLysProTyr...LeuLeuAspMETProProProGluLeuGlnAlaIleCys
PheAsnProCysThr...ThrMETGluGlnLeuGlnHisArgAsnLysHisHisPheArgPheSerArgThrSer
CysPheGlnSerGlyAsnAsnProTyrLeuLysProHisLeuCysLysIle...GlnTyrTyrIleHisAsnGln
LeuProMETHisGlnValGlyAsnSerSerHisThrAsnSerLeuProThrLeuArgAsnIlePheCysLeuTrp
TyrLeuSerLeuSerLeuPheGluTrpLeuPheArgIleTyrValLeuProLeuIleLeuSerAlaProTyrAsp
HisLeuHis...ThrArgPheIleGlnLeuCysHisIle...AlaProGlnGlnLysSerThrHisSerSerPhe
CysTyrArgSerArgSerAlaArgCysThrArgTyrTrpHisTrpArgTyrHisAsnLeuTyrSerValLeuLeu
GlnThrIleSerArgThrLysTrpGlyHisGlyThrGlyArgArgLeuProGlyHisLeuAlaArgSerThr...
LeuProSerSerSerSerProSerLysSerLysSerPheArgLeuAlaAsnArg...LysArgGlyAsnLeuPhe

FIGURE 21.1

IlePheArgGlyArgMETLeuLeuLeuCys...SerIleArgAsnArgHis...GluSer...ArgAsnSerArg

SerAsnThrThr...SerArgGlyAlaSerLysHisTrpThrLeuGlyProProGlnProMETAspAlaLeuAsp

SerProLeuLeuArgThrSerSerSerTyrAsnIleAlaThrProLeuTrpThrLeuTyrLeu...ProProCys

...LeuCysLeuPheGlnAsnArgSerCysLysThrThrAsnGlyAlaGlnAspAlaValGlnAsp...AspLeu

ProGlnThrProGlyProAlaCys...ProThrIle...Cys......HisGlnArgHisProSer...GlyAsn

LeuSerCysThrThrSerThrThrProGlnPheSerArgLysGlnLeuGluArgSerSerAlaAsnLeuProAsn

SerThr...ValPheLeuLeuArgTrpGly

FIGURE 21.2

TTGGTCTTAAGAACACAAATGATATGGCTCCAATGACTGGAGGAACACCAGGGTCCTTGG
TCTCACGCTGATTTAGATAAAACGACTGTCAGGCCTCTGAGCCCAAGCTAAGCCATCCTC
CCCTGTGACCTGCACGTATACATCCAGATGGCCTGAAGTAACCAAAGAATCACAAAAGCA
GTGAAAATGGCCTGTTCCTGCCTTAACTGATGACATTCCACCATTGTGATTTGTTCCTGC
CCCATCTTAACTGAGCGATTAACCTTGTGAAATTCCTTCTCCTGGCTCAAAACCTCCCCC
ACTGAGCACCTTGTGACCCCCGCCCCTGCCCCTAAGAGAAAACCCCCTTTGATTATAATT
TTCCACTACCCACCCAAATCCTATAAAATGGCCCCACCCCTATCTCCCTTCGCTGACTCC
TTTTTCGGACTCAGCCCGCCTGCACCCAGGTGAAATAAACAGCCTTGTTGCTCACACAAA
GCCTGTTTGGTGGACTCTCTTCACACGGACGCTCATGACATTTGGTGCCAAAACCTGGGA
TAGGAGGACTCCTTCAGGAGACCAGTCCCCTGTCCTTGCCCTCACTCTGTGAGGACATCC
ACCTACAACCTTGGGTCCTCAGACCAACCAGCCCAAGGAACAGCTCACCAATTTCAAATC
AGGTAAGCAGTCTTTTCACTCTCTTCTCCAGCCTCTCTTGCTACCCTTCAAACTCCCTCT
CTCACTACCCTTCAATCTCCCTGTCCTTCCAATTCCAGTTCTTTTTCATCTCTAGTAGAG
ACAAAGGAGACACATTTTATCCATGGACCCAAAACTCCAGCACCAGTCACGGACTTGGGA
AGACAGTCTTCCCTTGGTGTTTAATCACTGCGGGGACGCCTGCCTGATTATTCACCCACA
CTCCATTGGTGTCTGATCACGGTGGGGACACCTGCCTTGGTCACTCACCCACATTCCCTT
GGTGGTACGTCAACTGCAAAAGCAGGGGACGCCTGCTTTGGCTGCTCACCCACCCCCTTC
TCTGTGTCTCTACCTTTCTCTTTAAACTTACCTCCTTCACTATGGGCAAACTTCTGCCCT
CCATTCCCCCTTCTTCTCCCTTAGCCTGTGTTCTTAAAAACCTAAAACCTCTTCAACTCA
CACCTGACCTAAAACCTAAATGCCTTATTTTCTTCTGCAACACTGCGTGGCTGCAGTACA
AACTTGATAATAGCTTTAAATGGCCAGAATATGGCACTTTCAATTTCTCCATCCTACAAG
ATCTAGATAATTTTTGTGGAAAAATGGAAAAATGGTCTGAGATGCCTGACGTCCAGGCAT
TCTTTTACACATTGGTCCCTCCCTAGTCTCTGCTCCCAATGCGACTCATCCCAAATCTTT
CTTCTTTCTCTCCTGTCTGTTCCTTCAGTCTCCACCCCAAGCTCTGAGTCCTTTGAATCC
TCCTTTGCTACAGACCCATCTGAACTCTCCCCTCCTCCCCAGGCTGCTCCTCACCAGGCC
GAGCCAGGTCCCAATTCTTCCTCAGCCTCTGCTCCCCCACCCTATAATCCTTTTATCACC
TCCTCTCCTCACACTCAGTCCGGCTTACAGTTTCGTTCTGTGACTAGCCCTCCCCCATCT
GCCCAACAATTTCCTCTTAAAGAGGTGGCTGGAGCTAAAGGCATAGTCAAGGTTAATGCT
CCTTTTTCTTTATCTGACCTCTCCCAAATCAGTTAGCGTTTACGCTCTTTTTCATCAAAT
ATAAAAACCCAGCCAGTTCATGGCCCATCTGGCAACAACCCTTACAGGCTTTACAGCCCT
AGACCCTGAAGGGTCAGAAGGCCGTCTTATTCTCAATATGCATTTTATTACCCAATCCGC
TCCCAACATTAAATAAAGCTCCAAAAATTAAATTCTGGCCCTCAAACCCCACAACAGGAC
TTAATTAACCTCACTTCAAGGTGTACAAGAATAGAGTAGAGGCAGCCAAGTAGCAACGTA
TTTGAGTTGCAATTCCTTGCCTCAACTCTGAGAGAAACCCCAGCCACATCTCCAGCAAAC
AAGAACTTCAAAACACCTGAACTGCAGCAGCCAGGCGTTCCTCCAGGACCACCTCCCCCA
GGATCTTGCTTCAAGTGCCGGAAATCTGACCATTGGGCCAAGGAATGCCTGCAGCCCAGG
ATTCCTCCTAAGCCACGTCCCATTTGTGCAGGACCCCACTGGAAATCGGACTGTCCAACT
CACCCGGCAGCCAATCCCAGAGCCCCTGGAACTCTGGCCCAAGGCTCTCTGACTGACTCC
TTCCCAGATCTTCTCGGCTTAGCAGCTGAAGACTGACACTGCCCGATCACTTCAGAAGTC
CCCTGGACCATCACGGATACTGAGCTTCAGGTAACTCTCACAGTGGAGGCTAAGTCCATC
CCCTGTTTAATCGATACAGGGGCTACCCACTCCACATCACCTTCTTTTCAAGGGCCTGTT
TCCCTTTCCCCCATAACTGTTGTGGGTATTGACGGCCAAGCTTCAAAACCCCTTAAAACT
CCCCCACTCTGGTGCCAACTTGGACAACATTCTTTTATGCACTCTTTTTCAGTTATCCTC
ACCTGCCCAGTTCCCTTATTAGGCCGAGACATTTTAACCAAATTATCTGCTTCCCCGACT
ATTCCTGGGCTACAGCCACATCTCCTTGCCGCCCTTCTTCCCAACCCAAAGCCTCCTTCA
TATCTTCCTCTCATATCCCCCCACCTTAACCCACAAGTATGGGACACCTCTACTCCCTCC
CTGGCAACCGATCACACGCCCATTACTATCCCATTAAAACCTAATCACCCTTACCCTGCT
CAATGCCAGTATCCCATACCACAACAGGCTTTAAAGGATTGAAGCCTGTTATCACTTGC

FIGURE 22.1

CTGCTACAGCACGGGCTTCTAAAACCTATAAACTCTCCATACAATTCCCCCATTTTACCT
GTCTAAAAACCAGATAAGTCTTACAGGTTAGTTCAGAATCTGCACCTTATCAACCAAATT
GTTTTGCCTATCCACCCTGTAGCACCCAACTCGTACACTCTTTTGTCCTCAATGCCTTCC
CCCACAACTCACTATTCCGTTCTTGATCTTAAAGATGCTTTTTTCACTATTCCCCTGCAC
CCCTCATCCCAGCCTCTCTTTGCTTTTACCTGGACTGACCCTGACACCCATCAGTCCCAG
CAGCTTACCTGGGCTGTACTGCCGCAAGGCTTCAGGGACAGCCCTCATTACTTCAGCCAA
GCTCTTTCTCATGATTTACTTTCTTTCCACCTCTCTGCTTCTCACCTTATTCAATATATT
GATGACCTTCTACTTTGTAGCCCCTCCTTTAAATCTTCTCAACAAGACACCCTCCTGCTC
CTTCAACATTTGTTCTCCAAAGGATATCGGGTATCCCCCTCCAAAGCTCAAATTTCTTCT
CCATCTGTTACATACCTCGGCATAATTCTTCATGAAAACACATGTGCTCTCCCTGCCAAT
TGCGTCTCCAACTGATCTCTCAAATCCCAACCTCTTCTACAAAACAACAACTCCTTTCCC
TCCTAGGCATGGTTGGATACTTTTGCCTTTGGATACCTGGTTTTGCCATCCTAACAAAAT
CATTATATAAACTCACAAAAGGAAACCTAGCTGACCCCATAGATTCTAAATCCTTTCCCC
ACTCCTCTTTCCATTCCTTGAAGACAGCTTTAGAGACTGCTCCCACACTAGCTCTCCCTG
TCTCATCCCAACCCTTTTCATTACACACAGCCGAAGTGCAGGGCTGTGCAGTCGGAATTC
TTACACAAGGACCGGGACCATGCCCTGTAGCCTTTTTGTCCAAACAACTTGACCTTACTG
TTTTAGGCTCGCCATCATGTCTCCATGCGGTAGCTTCCGCTGCCCTAATACTTTTAGAGG
CCCTCAAAATCACAAACTATGCTCAACTCACTCTCTACAGCTCTCACAACTTCCAAAATC
TATTTTCTTTCTCACACCTGACGCATATACTTTCTGCTCCCCGGCTCCTTCAGCTGTATT
CACTCTTTGTTGAGTCTCCCACAATTACCATTCTTCCTGGCCCAGACTTCAATCTGGCCT
CCCACATTATTCTGGATACCACACCTGACCCTGATGATTGTATGTCTCTGATCTACCTGA
CATTCACCCCATTTCCCCATATTTCCTTCTTTTCTGTTCCTCATGTTGATCACATTTGGT
TTACTGACGGCAGTTCCACCAGGCCTGATCGCCACTCACCAGCAAAGGCAGGCTATGCTA
TAGAATCTTCCACATCCATCATTGAGGCTACTGCTCTGCCCCCCTCCACTACCTCTCAGC
AAGCCGAACTGATTGCCTTAACTCGGGCCTTCACTCTTGCAAAGGGACTACACGTCAATA
TTTATACTGACTCTAAATATGCCTTCCATATCTTGCACCACCATGCTGTTATATGGGCTG
AAAGAGGTTTCCTCACTACGCAAGGGTCCTCCATCATTAATGCCTCTTTAATAAAAACTC
TTCTCAAGGCTGCTTTACTTCCAAAGGAAGCTGGAGTCACACACTGCAAGGGCCACCAAA
AGGCGTCAGATCCCATTACTCTAGGAAATGCTTATGCTGATAAGGTAGCTAAAGAAGCAC
CTAGCGTTCCAACTTCTGTCCCTCATGGCCAGTTTTTCTCCTTCCCATCAGTCATTCCCA
CCTACTCCCCCATTGAAACTTCCGCCTATCAATCTCTTCTCACACAAGGCAAATGGTTCT
TAGACCAAGGAAAATATCTCCTTCCAGCCTCACAGGCCCATTCTATTCTGTCATCATTTC
ATAACCTCTTCCATGTAGGTTACAAGCCACTAGTCCACCTCTTAGAACCTCTCATTTCCT
TCCATCGTGGAAACATATCCTCAAGGAAATCACTTCTCAGTGTTCCATCTGCTATTCTAC
TACCCCTCAGGGATTGTTCAGGCCCCCTCCCCTCCCTACACATCAAGCTCGGGGATTTGC
CCCTGCCCAGGACTGGCAAATTGACTTTACTCACATGCCCTGAGTCAGGAAACTAAAATA
CCTCTTGGTCTGGGTAGACACTGTCACTGGATGGGTAGAGGCCTTTCCCACAGGGTCTGA
GAAGGCCACTGCAGTCATTTCTTCCCTTCTGTCAGACATAATTCCTTGGGTTGGCCTTCC
CACCTCTATACAGTCCAATAACGGAGCAGCCTTTATTAGTCAAATCACCTGAGCAGTTTT
TCAGGCTCTTGGTATTCAGTGGAACCTTCGTACCCCTTACTGTCCTCAATCTTCAGGAAA
GGTAGAATGGACTAATGGTCTTTTAAAAACACACCCCACCAAACTCAGCCTCCAACTTAA
AAAGGAGGATAGAGCCCAAAAACTCGCAACCAAGCTAGTAATTATGCTGAACCCCCTTGG
GCACTCTCTAATTGGATGTCTTAGGTCCTCCCAAATCTTAGTCCTTTAATATCTGTTTTT
CTCCTTCTCTTATTCGGACCTTGTGTCTTCCGTTTAGTTTTCAATTCATACAAAACCGC
ATCCAGGCCATCACCAATCGTTCTATAC**AATAAA**TGCTCCTTCTAACAACCCCACAATAT
CGCCCCTTACCACAAAATCTTCCTTCAGCTTAATCTCTCCCACTCTAGGTTCCCATGCCG
CCCATAATCCCTCTCGAAGCAGCCCTGAGAAACATAGCCCATTATCTCTCCATACCACCC
CCAAAATTTTTGCTGCCCCAACACTTCAACACTATTTTACATTATTTTTCTTATTAATAT

FIGURE 22.2

AAGAAGACAGCAATGTCAGGCCTCTGAGCCCAAGCCATCATATCCCCTGTGACCTGCACA
TATACATCCAGATGGCCTGAAGTAACTGAAGAATCACAAAAGAAGTGAAAATGGCCTGTT
CCTGCCTTAACCGATGACATTCCACCACTGTGATTTGTTCCTGCCCCACCTTAACTGAGC
AATTAACCTTGGGAAATTCCTTCTCCTGGCTCAAAACCTCCCCCACTGAGCACCTTGTGA
CCCCTGCCCCTCCACTACCCACCCAAATCCTATAAAATGGCCCCACCCCATCTCCCTTAG
CTGACTCCTTTTTTGGACTCAGCCCGCCTGCACCCAGGTGA**AATAAA**CAGCCTTGTTGCT
CACACAAAGCCTGTTTGGTGGACTCTCTTCACAGGGACGGGGGTGACAACAACACGGACA
CACATGGAGTGGTTTTAAGGAGCAGAGAGTTTAATACGCAAAAAAGAAGGAAGAGGCTCC
CCTGTACAGACACAGAGGGAGGGGGCTCCAAGCCGAGAGAAGGAAACCCCATGTGCAGTG
GAAAAGTGGTTGATTATACTGGGAGGCTGGAGGAGGCGGTGTCTGATTTGCACAGGGCCC
AGGGGATTGGGTTGACCAGGTGTATCATTCATGTACCCCGCAAAAAACCTGGCCCTCCCA
CCTCAGCCCTTTAATATGCAAATGTGGGTTGCCATGATGTTCTGAAAACACATGAATTAT
CTGGAGGGGGCCATGACACTTGGTACATGTGCTGACAAGAAGAGGGTGGGAATCGCCATG
GTGGCCATGTTGGGTGGACCTAGTTTTTAATAGCCTGCATTTGCATATCAAAGTTTGCTG
GCCTGGCTCTTTAAGCTGTCTTTTCTGTTAGAAAAGGAATGGTTTGGAATGGGTGAGGGT
TGCTTCTTATTACAAGAAAATTTCCAAAAACCTTTACTCTTTCTAGCTGCCAAAAAACTA
TTTCTTAATAACTTATGTATTACCATAATTAGGCAGCACCAAAGATCCCTGCAGGTCAGA
CCACTGCAATTAACATGCTGGCTTTACTGCTGATTATGGTAGCTGCATCCACCTAGCCTC
TCATATTGCAACTGCCTGACCTCTGCCACCCCACGAGCCACTTATCCCCACTTATAATCA
GCCCATTTCGATTGTAACATCTGCCACTTATTCCCGACGTTGTGGTATATCCTATAGATG
AATTCATTCAACATCCATTCCAACACCACCTCTCTTGCCTTCCTATACTCTCTGGAGAGT
GAATTACTGAGTCACATGATCTTCACTGCAGTCATTTGTGGCTATGTGACATAGTTCTGG
ACAGTGAACATAGACAGAAGT*CCCTGGGGCGGGCTTCCTTTCTGGGATGAGGGCAAAACG*

FIGURE 22.3

GATCTCTTGATCCCAGGAGGTCAAGGCTGCAATGAGCTAAGATCAAGCCACTGCATTCCA
GCCTGAGTGATAGTGGGAGACCTTGTCTTTAAAACACACACACACACACACACACACACG
AGGGCCTTTGACCACTCTTGAGTAGAAGACTCGAGAAGAACAAAGTAGAAGGCCAGAGAA
GAACAAAGTTACTTGAAAGATCTCTTATTAAAGAGAATGTACAAGCTATGAAAAAAAAAA
AACACACACACACACACAAACCTCATCTGGAATGAAAAAAACATAATGCATTTGGTTTCT
GGTTCCTTAGGCTGTTATGGAACAACCAAAGAACATTATTTGGTTTCTGAGGTCAGAAC
TATTTTATTCCCCTCAAGCACACTATGCTTATGGTTTGAGGGAGAATGAGAAATAGGAAA
CTAGGAACAGGCTGAAATGGTCTAATCTTGACCATCTAATTCTGCAGTGTCTTATTCTCA
TTCTAAAAGAGAATGGTTATATTCGCTGTTCTAGCATAAAAAGTAATGATAAAAATAAAA
GATCCCGTATTACCAGACAATAATCCCCTAGACTGTTTTAATGCTTGGTTGAGTATTTGC
TTATGATCTCAGACTTTAAAAGATGGTCTCCCCCTATGGTGAAGCTTGTTAATTATGTAG
GCATCATTAATGTCTGTTTACTTATCAAAATTTTATCATTGTTAGTTGTATTACTACTTG
ACAGTCCAATTTATTTAATTGAAAAGATTGGTTAACATTTTATAGTCAAAGTAATTGTTT
CCTGTGTTTTTTCCTGTTTAGGTTATTGGAGTGATGAGTAAAGAATACATACCAAAGGGC
ACACGTTTTGGACCCCTAATAGGTGAAATCTACACCAATGACACAGTTCCTAAGAACGCC
AACAGGAAATATTTTTGGAGGGTAAGTAAGGGAAATTTCTTCAGACCCATTAAATGTTAG
GAAAAAATGGAGCTAAAAGAGCTGGGTGGCTCACCTTTCTCATCCTGTGCTGAGAAATGC
TGGGGCTCACCCATAAGTATCCAGCATCCCCATGGACACAGGGAATTCTGAACAAATGTG
ATGAAACCGATGAAATGTCTGGCCTGTAGGTGGTTAGTGATGGAGATACGGGCTATATGT
GAATCTTGATTTTTGCAATTCATTAGAGCTTTGTAATGAAAGGAAACAGTTTGTTGCTTG
CTTTAAGGATAGGTTCATTTGCATTTCTCCGCAAGGAAGTAGTAATGAGTTACCAAGCCT
TAGATTTCACCCCTTTTTGATTTCTTGCTGACTTAACTTTAATTGAATGGAAGAGTTATC
ACAAATGAATTATCTTTTTGGTTTTTTTTTTTTGAGATGGAGTCTCACTCTGTCACCAG
GCTGGAGTGCAATGGCATGATCTCGGCTCACTGCAACCTCCGCCTCCCAGGTTCAAGCAA
TTGTCCTGCCTCAGCCTCCCGAGTAGCTGGGACTAAGGTGCGCGCCACCATGCCCAGTTA
ATTTTTGTATTTTTAGTAGAGACGGGGTTCCACTATGTTGGCCATGATGGTCTCGATCTC
TGGACCTCGTGATCCGCCCACCTTGGCCTCCCAAAGTGCTGGAATTACAGGCAAGAGCCA
CCGCGCCCAGCCAGGAATGACAAATGAATTACCTTATAAGTAAATGCCATTAAGGAAGGA
TAGCTGGAAGATGGGTTGAGGGGAATGGAGGACCACAGAACTAGTCCTATTTAAATACAT
GTGCATGGTAAAATGATTCCATTTGACAATAGGTTAATTATCTCATAGCATAAGGAAAAT
GCTTAACAGTCATATGCAAGATGATAAGCTTTCCTATAGCATCCAACCAAAAGATCTAGC
CAGTACAATTTCCTTTGCTATATTAGGGTTAGAAAGGCCCCCAGAGGTGAACCAATTAGA
TGGAATCCTTGAATAAAACACTGGATTAGCAGTGAACAGAAAAAAGTCAGATTGCTTTCC
TTCTTCCCATAGATGTCTCAGGGATATTTAGTTTCCTCAGAAGATAAAGAATTTAGTAAG
CGTTTTTTTGTGCATACTTACATGAAATGTACATTATTTGAATTCTTTAAAAAGAAACAG
CTGCATGATAACAAAAATTGTGTTATGCTTGCTTTAGCTGGTATTTTTGCCTAGAACGAT
TATATCGTTCGGACAAGAAGCTATTCCTAAGAAACAATATTTTTAATCCAGGAAGTTTTT
CATTTTTAGAAATTTATCTTACTATTTCCCAAGCAAAAGAGGGTAGTTACAGATTCACTA
AGAATCATGTGCTCACAATTTTTATTTAATAATTATTCCTCCTTAAAATATATTAATCAC
CTGACTTACAATGGTGGAACCATGAGTGCATTTTTGCCTTTATTGTCAATAACGTCTTCT
CAGAAGTGAGCCACAAAGGTGCATAGTTCTTGGAGTTAAAGGTCTGAATTAAGACAATCC
AGCATAAGTCTCATTAATGTGTGATTATTTGAGAAAAGGCAAGAAGTACCTAAGAATCT
CCCCCTCACTGTCCAGTTCCCTGTTTCATTTAAAGATTCACTGTAAGTAACTGAAAGGCT
TTCCTTGGGAGGATTTATTTGAATCAGTCTTTCACATGCAAAGGATATTGTAGAACATCT
CGTTTTTGCTGGCAGGAATATGAACATCTGTTGTGAGGAAAGAAAAAGTTTCATGCAAAT
TACACTGCCAAAGAAGGGATGTTCAAGTTGAGAAACCAGTGACATTTCTTGTAACTGTAC
TATGAATCAGCGCATTTTAATCTTCTAGATAATATATGGAAGTGCAGGAAGGTGGTAGGA
AACGGTGTTCATTTTACATATGCGTTATTTTATTCTGTGTGAGTGACTTCATGGCACCGA
CATTGCTGTTTTTAAATGAGGATACAGTAAATTGCAGTCCGAGGAAGGCTAACTGGAATC
AACATACCCGTAGCTTTAGAAAGCAGTTTCCGCACCAGCGAAGAGTACAAGAGCGATGGA
ACCCCATGTTCCTGGAAGTTTGCACATCAGAGTAAACAAACTTGAAAACCCCTCTTGATA

FIGURE 23.1

GCAGAATTCACCCAGCCTTGTTCCATTTTCTCTTAACAAAACACACCGCAAAAGCTCTCA
CAAGCTGCTTTGATGAAGCCACATGTATTTCCCCCTTCACAATTTACAGGAAGTTACTCT
TAAAAGAAAGTGATTCTGGTGTTTACCGCCTGTGTTAAAGGGACAGAGTTCCTTTTTATT
TCTGATAACGTTTGAGCGAAATACAGAAACTATCTGTAGACTAGCATAGTCGGTACGTGA
GTAAGGAAAAGCAATAACCTGCTGTCCGGTGAGCACAAAATTCCTGCTACGAACAGTGCC
TTACTGCTGCTTGGAGACTGCAAGTCGCAGATCACACTAGGTATTGACTGATTGTATAAG
GAAATTTCTTAAAGTCTAAAGTAAAGGTGGTACCTCCTAAAAAGAGGGGAAGAGAGAAAA
CTTTGTGTGGAAGGATAAGGAGTGTGTTTATAGTTTCAGTAAGAGTGTACGTTTTAATTT
TTCTTCTTCCTCTGCCTCTTTGCCAAGTAGCCTGAGTGCATCTGTTATCCAGAAGTAGTA
TTACTCTAGGACAAACTTCAAATTCTTCATTCTGCGTTGCCTTTAAGGAACAACATACTT
TCTTCCTGTTCTTTTTCCAAAAACACACGCCTATGGCTCTGTGTGTGGTGTTTTAGCCAG
CCTCCTCCCAGATAAGGGGTTCCCTTCCCTCCTTTGCATTGAAAGGAAAGTGCAAGTCTG
GACATGTTTATCAAGAGGAAAAGTGACTTCTCAGTAATAGACTGTCAAATTCGGGCTGCT
GCCCGAGTGTTCGCTTTGTTATGGCAGGTGAAGTTCACCTTTGCCCCACCCAGTGTTTCC
ACAAAAAGGCAAGGTTCCAAGTATTCATATGAACAAGTGTTACTTTAGGACTTGGAGGGT
TGGGGGTGGAGGATGTTTGCATAGTTGAAGCCTTGGGCGGGGGTGTAGGAAACGGCGAGT
ACAGAGGCCATAGAAAAAGCTAAGACTCAGTTTGACGTCGTCAGCCGGCTTGGTCTTCTA
CCCAGTGACTCAAAGCACTAAAAGTCAGCATAATCGGAACTGAAGTCAGTAGCATCGCCC
ATTTGCCATTCACTGCAGTAGCAAAAGTAGTACTCTGTGGTGGGTTAATCGGTTTGAGGC
AGCTCCTTAAATGAACATTTGTGTTTCATTTTTCTGTTATTTTCCCGAACATGAAAAGAC
GATAAAACTGAAATGGAAAAGGTAACTGACAAAAGTGTGCCTTACCTGTTTCCGCCCTGA
TTTCTGCTGATTCAAGACTATTCTGGCTAAACTGATTGGATTCTTTTTCTAACTAGGCAG
TAGGGGATCAGAAATCACACACGGTACCGGCTGTGTTTATTCTGAGAGGTGCTGGGGAGC
TTTGGGTCTGACTTCCTTTTACATGCCTGTCTTCTCTTTTGGACAGATCTATTCCAGAGG
GGAGCTTCACCACTTCATTGACGGCTTTAATGAAGAGAAAAGCAACTGGATGCGCTATGT
GAATCCAGCACACTCTCCCCGGGAGCAAAACCTGGCTGCGTGTCAGAACGGGATGAACAT
CTACTTCTACACCATTAAGCCCATCCCTGCCAACCAGGAACTTCTTGTGTGGTATTGTCG
GGACTTTGCAGAAAGGCTTCACTACCCTTATCCCGGAGAGCTGACAATGATGAATCTCAG
TAAGTGGATTACAGAACAAAAAAATAAAAAATGCCAGTAATGTCGGTTCTGCCCCTTTGA
ACTAATAACATGTTGTTTAATTATACGGCTTTGTCATGTGTTGGATGAAGTAGGTGGCTT
AAGCTAGGGACTAGGAAGAGGAAAAACATTTTTTGAGTCCCTATTAACTATTAGGAAACT
TGATCATTTAAAAGTATATATATATATGAGGAGCTACCTTGAGTTTTGAATTCAGGATGT
TACAGGAAGAAATATATGTCCAATTCTAATTTATCCAAAAGCAGTTGGGAGAATTACAGG
GATTGGTCCAGACATGCTGCGTATGCAAGGTATAGCCCTCATCTGTGGTACTTTGGCAGG
GCTTAGACTGCATCAAAATATTTATAGATGTACATTTGAGTGTACAGTTAGGATCTGATG
TGGAACATTGTAAGATCATTGCTAGAAAAACTTTGTCATAATTTTTCAATATTATTCTAA
GTGAATAACCGTAAAGATTTTACATCTTAGCTTCCTTCCTTACAGTAAAAAAACTATCTG
ATCTCTTGATCAGTATTATAGTAGCCACCTATCACTTTATCTTAACAAATTCTCAATTCC
TTAGGTTTATGTGCTTTTACTTCTTTTATTTGATTAAAATTGCTGTCATGACCTCTCTCT
GCAGAGGGCTGCATCATTTTGGTCATTCTCAAGTGATCTCTTTGAGCAATTTAAGAATTG
CCATAAGATTCTAACCTCTGCTGTAACTATGGTTGTGTGTTCTTGGTTAGACCACTAAAT
CTTATTAGCAGTTTTAAAAATTATTCCTTTTGGTTTAGAAGTTAAGACTAAATGCTGAAG
TTTTTGTAACTTTTGGTTTTGATATCATTTCAAACTTAAGAAAACATTTGAAGAAAAGGA
CAAAGAATTTCCACTTACCCTTTACCCAGGTTTACCAGTTATTGATAAGTATATCCATTT
GCTTTACCAGAAGGCTAACTTGTTTTAGTTCTCATTTTCACCTTTGAGACATTTGGAATA
AATATCAATGTTAACATAAATTGGAATTTTGACTTTGATTTAGGACCAATGAACAAGCC
AAGTACTTACCCTAGTCATATATAATCCAACTGTATGGTTATTTGGTATTCATTCCACAC
TTCATTTTACTTGATCTCCCTTAAGATTGCAAGATTGTGTTTGCAGTTTTTCTGAAAATC
TGGGGCTATAAAAGCATCAGGACCTCCCCCGTAGGGGAGGTCGTGTGTTTGGGGTCCTTA
CACAACAGGTTACCCTTGAGCTTCAGGAAAAGAACTGGCTCTCAGTTCCCCAGTTCCAGC
TTAATGGGTCTAATTAGGTCCTGACCAAAAAGGTGGCAGTTCTTTTCCCTCATGTCTCTT
CAGCGCTCCCCGAGACTCTGGAGACTCTGTCATATCCCTAGGGCTGAGCCTCCCAGGAAC
CATTCGGCTGTTGTGGCATCTGTGTATGCCATGCCCAGTGCTGAGGACCTAGTAACAAAC

FIGURE 23.2

GACAAATGCACAGGCACAGTGGCATTTTTGTGGAACTCGTATTCCAGCTGTGCGTCTCAG
AAGAAGCGCACAGCTCCCTCCTGGCTTTCTTAACATAGTGAGCCACTTCCACTTAAGGGT
CTCCTTACATTCCTTGAGTTTAATCATTCATGGATTCAGAGGAAAGTCTTTTGATTTTTG
CTTTTCTTTAAACAGTTCATTTGAGGTGACCTACCCCAGTGACTTTGCACCAACCACCAA
GAAACTTTTTTGCATGCTTCCCGCACCCTGTGCCAATCAAGGGAAGGGTTTAAAGGCCTG
GCGTTTTTATTCCTCAAAGAAAGGTTTTGCACAGTATTTTAAGGTTCAAGTGCTTCTACT
TTGTGTTCAGAAGCAACTGTCATATATACTGTGAAATGACACCTTTTATTTATCCCTTTT
TATTTATGCAGTATGTCCCCTTTTATTTTGGCAGAATTTTTTCTAAATGGTGGTTTAACA
TTTTCAAGCACATTTCATTGTCCAATATTCATAGTAAAGAATGAGAGTTAACAATAACCA
GTCACATTAAAACAAGATTCCTGCTGCCAGTTGTGAAACCGGTTGTCTTAGGCGTGGCAG
CTGATGATTGAGACTGTGATCAGGAAAATTTCCACTATTTCATCAGGCCTAATAGGTAGA
TTGTGTCTCCAAATGAACTGTGTTGGGTTTCCATGCTTAAAGCACAATAGAGGTGGTGCA
AGAATCTCCATGAGGGCTTAAATGGCAGTGATGGTTCAGGCGGTAGAGTTTGGAGAAGAA
GGGATTTGAAACAAACCAAAGGAAAGAAAAGTAAGTAGCCAGAAATCACAAAATGGCATT
TTTCTAAAAACAAAGGAAAAGGAATAAAAGAACTAATAAGTTTGAAACCCCTACCCCTCC
CAAATTTGGCAGGGGGGGAGGTATTTTTTTTCTATCTATCTAACTAACCCATCTAGAAAA
CAGTTGACCAAATTATAGACTTCTAAATGTTAATCTGCTTTCTCAGTTTCAGTTGAAAAG
AGACTTTGTTTTGCCTACTGCAGAACTTCTAGGTTCTTTCTTATAGTCTTGGGGTTCTTA
TTATAGATCGAAAATGTGAGTCGGCATAATTAAGCCATTCGGAGTCTTCAGAAGCAGTTC
ACTCTTGAAATGACTCCGTCCGCCTACAGCCATTTAAGATTTCAGAACAAAAACAGATCT
TGATTTTCTTTTTCATGTTAACTCAAGCTGTTGCTGAGTGGGAGAGTCAGAAATGACACC
AGCTCCACTGATTACTCAGCTGCTGAAGGATGATTTTTTAAAATGCACCTTTACTGTATA
TGGACTTCCTAATTTCCACCTGTAGAGCATCTTAGGGAGGCTAACATGTCACTCTGGATG
TTCTTTTAGAATAAGATGCAAATCTATTTTTCTGAAGGCATTAGAGATAGCAAACATTTA
TTGTGAGTTTACTATATACTAGGCACTGTGCTAAGTGTTTTGCATAGAAAGTTTAAAATT
CTGGCTTTTTTGTTGGCCCAATCATAAGTTTCATATCAGTTCAACATTCAAATTATATTA
AGGTACTTAAGAAGAATCCCTGGCTAAATGTGAGGGGCAGTGCCACAGATGGACTGAAAC
TTTATGCTTATTGCACATTTATGCTATTATTATTTGTTGAATTATAGAACCAAGGGAGTG
TGGAAGCCACTGGAAAAAATATGAGACTTAGATACATAATTTGAGTAAAAATGGCTCAAA
GTCATGAGGGTAAAGTTTTTTGTATTTCCATTTTATTCGAGCGGCATCGTTTTTAAAAAT
CATTATGAATTTGACCCTATATAGATGTTTCCAAATAATTCTTTTTCACCTTCATAAAAT
TCCTTCCTGTGGCTGTGAGATGCCTTGCCTATCAGTTTTCAAGCTTAGTTGTCTTTCTCA
TCCTTTACCATTTTAGCTTTAAAAAACAAAAGTGACAATTAGAACTTCCTGCCTGCTGGG
CCTCACTGAAAGACCGATATTGGCCTGATAAGGAGATATTTATTTTGTTTTAGTGGCTTC
AGAAATCCCTCTCCCTCAGCAAGCTTTCCATCACGGCCCCCCCGTCAGCATCTTCCCTGA
TAGCGTTCTTCTCTGTGTTTATTCTGGGGCTTCAGGCTCGCCCAGGAGGAACTGATAACC
GCTGGCAGGAGATAACATTCTCTAAGGGGCTCTCAAATTGGAATCGAATCCCTCAAGCCA
GTCAGCCTAGAGAATACATTTAAAGGGTTCAGTTCTGGAGTTTCACAGAGTTCATTTCTA
GACCTATCAGATAGCAAGTGTGGAGTTCTTTCTCAACTAAATTCAAGCAGAGACATTTTT
TAGACGATGAAGGATATTTGCACAAAGGCTTCAGCATGATCCCCCAAACCTGCTGCCTCT
GAAGGCATCTCCACACATTGACAGCCAATGCCTTCAGTGCGTTCCTAGGGCAGGTGTCCT
GGCTTGAGTGACTGTCCTCCAATAATCAGAGCTCAAACTAAACATCGTATGTTTTACTTT
TGGTTTCCAGGCAAGGCTGAGCAGGGAATTTTCAGTTTTCCCTGCCCAGATGGGTGTTTT
TTCCTGAAGGCATCATTTATTGTGTAGCGAGGAGACAGGGCTGGCTGTGGCAGGGATAGT
CTAGAACTGTCCTCATTGCTGCTGTTCCTAAATAGTATCTTTACCAAGTAATAACGTGCC
GTCTTTGGGAATAAGTGCTTTCCTCTTAGCCTGTTCTGTTTTCTTGGGTGCGCTAAGTAA
TTGAACTGGCTCAGGAAGTACCTATTGTGGTTTGGCAGAGGTGACTGTCACGCCTTGTGA
CTCCAGGGGCCAGCACTGCTGGGATCCTGGCTAGACCAGACAGAGCCTTGGTGAAGTGCT
TAGGCTGTCTGCACATCGCGAGGAAGGTGGTATTCACTTCGCTAAGCTCCTTGGCATAGG
CAGTTTGAACAGGGCTTTATCAAATTCGTATTCAACAAGAGTAGAAGCGAAAATTGATGA
CTGTGTATTACTTGAAATGAGTCTTAATCTTTCACATTTAGTTCTCAGGGTATGCTGATT
TCCTTTAGGTAAACCATGAACATCAGAAAGACTTTTATTAACCTATGACAGGGTCCCCAC

FIGURE 23.3

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CCCAGTATTTTTCCACTCCATTAAAATGGAAGTTTTTTTTTTTTTTCTTTTTTGAGAC
AGAGTTTTGCTCTTGTTGCCCAGTCTGGAGTGCAATGGCACAATCTCGGCTCACCACAAC
CTCCACCTCCCAGATTCAAGCGATTCTTCTGCCTCAGCCTCCCAAGTAGCTGGGATTACA
GGTGTGCGCCACCACGCCCAGCTAATTTTGTATTTTTAGTAGAGATGGGGTTTCTCCATG
TTGGTCAGGCTGGTCTCGAACTTCCGACCTCAGGTGATCCGCCCACCTCGGCCTCCCAAA
GTGCTGGGATTACAGGCAAGAGCCACTGCATCCAGCTTAGGCTATCTTACTCCAGCCTAA
ACAGCAATTTTCTATCATAAGGTCTGTACTAATGAAAACAGAATCACCCAAGGCTGCTGT
TTGTTCTGTCTGTGCTGCCATTGTCCGCATTTTGCTGAGGAGGAAACGGAACTGCACTTT
TGAGTGAGTGGCCCAGAGCCTTCTAGAATGAGAGTGCGTTGGAAGCCAGATATGTGGCGA
TTGTGTCGCCAGCTGTTACTCAGGTTTTCTCAAGAAGGAGGAGCAACTTTGGCAGTTTTG
CTTCAGTTCTCTCTAGCCCTCTGTGTAATCGCCCCTTTTTCTTTATTTCAGCACAAACAC
AGAGCAGTCTAAAGCAACCGAGCACTGAGAAAAATGAACTCTGCCCAAAGAATGTCCCAA
AGAGAGAGTACAGCGTGAAAGAAATCCTAAAATTGGACTCCAACCCCTCCAAAGGAAAGG
ACCTCTACCGTTCTAACATTTCACCCCTCACATCAGAAAAGGACCTCGATGACTTTAGAA
GACGTGGGAGCCCCGAAATGCCCTTCTACCCTCGGGTCGTTTACCCCATCCGGGCCCCTC
TGCCAGAAGACTTTTTGAAAGCTTCCCTGGCCTACGGGATCGAGAGACCCACGTACATCA
CTCGCTCCCCCATTCCATCCTCCACCACTCCAAGCCCCTCTGCAAGAAGCAGCCCCGACC
AAAGCCTCAAGAGCTCCAGCCCTCACAGCAGCCCTGGGAATACGGTGTCCCCTGTGGGCC
CCGGCTCTCAAGAGCACCGGGACTCCTACGCTTACTTGAACGCGTCCTACGGCACGGAAG
GTTTGGGCTCCTACCCTGGCTACGCACCCCTGCCCCACCTCCCGCCAGCTTTCATCCCCT
CGTACAACGCTCACTACCCCAAGTTCCTCTTGCCCCCCTACGGCATGAATTGTAATGGCC
TGAGCGCTGTGAGCAGCATGAATGGCATCAACAACTTTGGCCTCTTCCCGAGGCTGTGCC
CTGTCTACAGCAATCTCCTCGGTGGGGGCAGCCTGCCCCACCCCATGCTCAACCCCACTT
CTCTCCCGAGCTCGCTGCCCTCAGATGGAGCCCGGAGGTTGCTCCAGCCGGAGCATCCCA
GGGAGGTGCTTGTCCCGGCGCCCCACAGTGCCTTCTCCTTTACCGGGGCCGCCGCCAGCA
TGAAGGACAAGGCCTGTAGCCCCACAAGCGGGTCTCCCACGGCGGGAACAGCCGCCACGG
CAGAACATGTGGTGCAGCCCAAAGCTACCTCAGCAGCGATGGCAGCCCCCAGCAGCGACG
AAGCCATGAATCTCATTAAAAACAAAAGAAACATGACCGGCTACAAGACCCTTCCCTACC
CGCTGAAGAAGCAGAACGGCAAGATCAAGTACGAATGCAACGTTTGCGCCAAGACTTTCG
GCCAGCTCTCCAATCTGAAGGTAGGCCTTGAGAGAGAGCAGTCCAAGGGGCTGTGAGTGC
ATGCTTGTGTTTGTATTTAGCTTGCTTTCCATGGGGTATCGATTGCATTTGCAGTAGTAT
GAGCCCCCGGTTGGGGATAGTGGGTATGGATTCCGCCTGGCTTTTGCCACTTCTAGCTCT
TTGACTTTGGACAAGTGACTTCCCTTCTCCTGATTTTCTTCTGAATAATAAAAAAATTAG
GGGTTTGGACTAGAAGATTAGGTGAAACTCCCTGCTAGCCTGTGATTTTTGTGCTTTTAA
GAAAAACACCATTCTGAAAACATGAAGATTTCTTCTTTTTAAGACTGTCTTGATGCTTTT
CTTAAGATATTTGCATCAACACTTGAGTCTTGGAGCAGAAATGTTAGGTCTCAGAGCCAG
CTTGAGAGCAGAGCTAACACATGTGGCTTCTTCCCAGGTCCACCTGAGAGTGCACAGTGG
AGAACGGCCTTTCAAATGTCAGACTTGCAACAAGGGCTTTACTCAGCTCGCCCACCTGCA
GAAACACTACCTGGTACACACGGGAGAAAAGCCACATGAATGCCAGGTGCGCAGTATTTT
CTGGGTAGACCTTCTGACCTTTGTAGAAAATGTCTGTGAGTCACCCTCCCATGTCCTATA
TAGCCCGTAGTTAAAGCCAACACCAGATTCTGCGTTGTCCCATCCTGGACTGATGGCACT
ATGGTCCTTCCCAGTACTTTGTATCTGCTGATGACTTGAGATGGCACAGCCAGCTTCCAG
TGGGTGGAAAATGGTAGGGGAAATAAACAGCCCCTCGTGTGCTGTGTGCCCACATCCCC
CCGTTTGCTTAATACCACACTGGAGGTGCCACAAGGAGGCTTCTCACCTCCTAGGTTGCT
GGGCGTTGGCCGGTAAGCCTGCCCCTCCCGTTGGCAACTCTTAATCTTCTGGCCTTCCTG
TCTCCCTTCCCTGCTGTCTCTCTCCCCTACACTGTAGGTCTGCCACAAGAGATTTAGCAG
CACCAGCAATCTCAAGACCCACCTGCGACTCCATTCTGGAGAGAAACCATACCAATGCAA
GGTGTGCCCTGCCAAGTTCACCCAGTTTGTGCACCTGAAACTGCACAAGCGTCTGCACAC
CCGGGAGCGGCCCCACAAGTGCTCCCAGTGCCACAAGAACTACATCCATCTCTGTAGCCT
CAAGGTTCACCTGAAAGGGAACTGCGCTGCGGCCCCGGCGCCTGGGCTGCCCTTGGAAGA
TCTGACCCGAATCAATGAAGAAATCGAGAAGTTTGACATCAGTGACAATGCTGACCGGCT
CGAGGACGTGGAGGATGACATCAGTGTGATCTCTGTAGTGGAGAAGGAAATTCTGGCCGT

FIGURE 23.4

GGTCAGAAAAGAGAAAGAAGAAACTGGCCTGAAAGTGTCTTTGCAAAGAAACATGGGGAA
TGGACTCCTCTCCTCAGGGTGCAGCCTTTATGAGTCATCAGATCTACCCCTCATGAAGTT
GCCTCCCAGCAACCCACTACCTCTGGTACCTGTAAAGGTCAAACAAGAAACAGTTGAACC
AATGGATCCTTAAGATTTTCAGAAAACACTTATTTTGTTTCTTAAGTTATGACTTGGTGA
GTCAGGGTGCCTGTAGGAAGTGGCTTGTACATAATCCCAGCTCTGCAAAGCTCTCTCGAC
AGCAAATGGTTTCCCCTCACCTCTGGAATTAAAGAAGGAACTCCAAAGTTACTGAAATCT
CAGGGCATGAACAAGGCAAAGGCCATATATATATATATATATATATCTGTATACATATTA
TATATACTTATTTACACCTGTGTCTATATATTTGCCCCTGTGTATTTTGAATATTTGTGT
GGACATGTTTGCATAGCCTTCCCATTACTAAGACTATTACCTAGTCATAATTATTTTTTC
AATGATAATCCTTCATAATTTATTATACAATTTATCATTCAGAAAGCAATAATTAAAAAA
GTTTACAATGACTGGAAAGATTCCTTGTAATTTGAGTATAAATGTATTTTTGTCTTGTGG
CCATTCTTTGTAGATAATTTCTGCACATCTGTATAAGTACCTAAGATTTAGTTAAACAAA
TATATGACTTCAGTCAACCTCTCTCTCTAATAATGGTTTGAAAATGAGGTTTGGGTAATT
GCCAATGTTGGACAGTTGATGTGTTCATTCCTGGGATCCTATCATTTGAACAGCATTGTA
CATAACTTGGGGGTATGTGTGCAGGATTACCCAAGAATAACTTAAGTAGAAGAAACAAGA
AAGGGAATCTTGTATATTTTTGTTGATAGTTCATGTTTTTCCCCCAGCCACAATTTTACC
GGAAGGGTGACAGGAAGGCTTTACCAACCTGTCTCTCCCTCCAAAAGAGCAGAATCCTCC
CACCGCCCTGCCCTCCCCACCGAGTCCTGTGGCCATTCAGAGCGGCCACATGACTTTTGC
ATCCATTGTATTATCAGAAAATGTGAAGAAGAAAAAAATGCCATGTTTTAAAACCACTGC
GAAAATTTCCCCAAAGCATAGGTGGCTTTGTGTGTGTGCGATTTGGGGGCTTGAGTCTGG
GTGGTGTTTTGTTGTTGGTTTTTGTTGCTTTTTTTTTTTTTTTTTTTTTAATGTCAAAAT
TGCACAAACATGGTGCTCTACCAGGAAGGATTCGAGGTAGATAGGCTCAGGCCACACTTT
AAAAACAAACACACAAACAACAAAAAACGGGTATTCTAGTCATCTTGGGGTAAAAGCGGG
TAATGAACATTCCTATCCCCAACACATCAATTGTATTTTTTCTGTAAAACTCAGATTTTC
CTCAGTATTTGTGTTTTTACATTTTATGGTTAATTTAATGGAAGATGAAAGGGCATTGCA
AAGTTGTTCAACAACAGTTACCTCATTGAGTGTGTCCAGTAGTGCAGGAAATGATGTCTT
ATCTAATGATTTGCTTCTCTAGAGGAGAAACCGAGTAAATGTGCTCCAGCAAGATAGACT
TTGTGTTATTCTATCTTTTATTCTGCTAAGCCCAAAGATTACATGTTGGTGTTCAAAGTG
TAGCAAAAAATGATGTATATTTATAAATCTATTTATACCACTATATCATATGTATATATA
TTTATAACCACTTAAATTGTGAGCCAAGCCATGTAAAAGATCTACTTTTTCTAAGGGCAA
AAAAAAAAAAAAAAAAAAAAGAACACTCCTTTCTGAGACTTTGCTTAATACTTGGTGACC
TCACAATCACGTCGGTATGATTGGGCACCCTTGCCTACTGTAAGAGACCCTAAAACCTTG
GTGCAGTGGTGGGGACCACAAAACAACCAGGGAGGAAGAGATACATCATTTTTTAGTATT
AAGGACCATCTAAGACAGCTCTATTTTTTTTTTGCCACTTTATGATTATGTGGTCACACC
CAAGTCACAGAAATAAAAAACTGACTTTACCGCTGCAATTTTTCTGTTTTCCTCCTTACT
AAATACTGATACATTACTCCAATCTATTTTATAATTATATTTGACATTTTGTTCACATCA
ACTAATGTTCACCTGTAGAAGAGAACAAATTTCGAATAATCCAGGGAAACCCAAGAGCCT
TACTGGTCTTCTGTAACTTCCAAGACTGACAGCTTTTTATGTATCAGTGTTTGATAAACA
CAGTCCTTAACTGAAGGTAAACCAAAGCATCACGTTGACATTAGACCAAATACTTTTGAT
TCCCAACTACTCGTTTGTTCTTTTTCTCCTTTTGTGCTTTCCCATAGTGAGAATTTTTAT
AAAGACTTCTTGCTTCTCTCACCATCCATCCTTCTCTTTTCTGCCTCTTACATGTGAATG
TTGAGCCCACAATCAACAGTGGTTTATTTTTTCCTCTACTCAAAGTTAAAACTGACCAA

FIGURE 23.5

GTCTGGACTTGTGGTGCGCTGCCAGGGATCCGCAGCGTTGCCGGTTGTATTCGCTGGATACCAGAGGGCG
GAAGTGCAGCAGGGTTCAGCTCCGACCTCCGCGCCGGTGCTTTTTGCGGCTGCGCGGGCTTCCTGGAGTC
CTGCTACCGCGTCCCCGCAGGACAGTGTGTCAGGCGGGCAGCTTGCCCCGCCGCCCCACCGGAGCGCGGA
ATCTGGGCGTCCCCACCAGTGCGGGGAGCCGGAAGGAGGAGCCATAGCTTGGAGTAGGTTTGGCTTTGGT
TGAAATAAGAATTTAGCCTGTATGTACTGCTTTAACTCCTGGAAGAATGACAGATGACAAAGATGTGCTT
CGAGATGTGTGGTTTGGACGAATTCCAACTTGTTTCACGCTATATCAGGATGAGATAACTGAAAGGGAAG
CAGAACCATACTATTTGCTTTTGCCAAGAGTAAGTTATTTGACGTTGGTAACTGACAAAGTGAAAAAGCA
CTTTCAGAAGGTTATGAGACAAGAAGACATTAGTGAGATATGGTTTGAATATGAAGGCACACCACTGAAA
TGGCATTATCCAATTGGTTTGCTATTTGATCTTCTTGCATCAAGTTCAGCTCTTCCTTGGAACATCACAG
TACATTTTAAGAGTTTTCCAGAAAAAGACCTTCTGCACTGTCCATCTAAGGATGCAATTGAAGCTCATTT
TATGTCATGTATGAAAGAAGCTGATGCTTTAAAACATAAAAGTCAAGTAATCAATGAAATGCAGAAAAAA
GATCACAAGCAACTCTGGATGGGATTGCAAAATGACAGATTTGACCAGTTTTGGGCCATCAATCGGAAAC
TCATGGAATATCCTGCAGAAGAAAATGGATTTCGTTATATCCCCTTTAGAATATATCAGACAACGACTGA
AAGACCTTTCATTCAGAAGCTGTTTCGTCCTGTGGCTGCAGATGGACAGTTGCACACACTAGGAGATCTC
CTCAAAGAAGTTTGTCCTTCTGCTATTGATCCTGAAGATGGGGAAAAAAAGAATCAAGTGATGATTCATG
GAATTGAGCCAATGTTGGAAACACCTCTGCAGTGGCTGAGTGAACATCTGAGCTACCCGGATAATTTTCT
TCATATTAGTATCATCCCACAGCCAACAGATTGAAGGATCAACTATTTGCCTGAACAGAATCATCCTTAA
ATGGGATTTATCAGAGCATGTCACCCTTTTGCTTCAATCAGGTTTGGTGGAGGCAACCTGACCAGAAACA
CTTCGCTGCTGCAAGCCAGACAGGAAAAAGATTCCATGTCAGATAAGGCAACTGGGCTGGTCTTACTTTG
CATCACCTCTGCTTTCCTCCACTGCCATCATTAAACCTCAGCTGTGACATGAAAGACTTACCGGACCACT
GAAGGTCTTCTGTAAAATATAATGAAGCTGAAACCTTTGGCCTAAGAAGAAAATGGAAGTATGTGCCACT
CGATTTGTATTTCTGATTAACAAATAAACAGGGGTATTTCCTAAGGTGACCATGGTTGAACTTTAGCTCA
TGAAAGTGGAAACATTGGTTTAATTTTCAAGAGAATTAAGAAAGTAAAAGAGAAATTCTGTTATCAATAA
CTTGCAAGTAATTTTTTGTAAAAGATTGAATTACAGTAAACCCATCTTTCCTTAACGAAAATTTCCTATG
TTTACAGTCTGTCTATTGGTATGCAATCTTGTAACTTTGATAATGAACAGTGAGAGATTTTTAAATAAAG
CCTCTAAATATGTTTTGTCATTTAATAACATACAGTTTTGTCACTTTTCAAGTACTTTCTGACTCACATA
CAGTAGATCACTTTTTACTCTGTGTTACCATTTTGACTGGTCGTCATTGGCATGGGGTGGATATAGGGCA
TAGGATTACTTGTCTCAGAAGCTGTCATAGAATTTCTTGCTGCCAATTAAAAAACCTGTGTTCTTTACAC
ACTACACGTATAAATATTGTAACTGTTCATCTTTGTTGTTTTATCACTGTAAGCCTGTCAAATCATAGTA
TCCTAAGCATCTGTAAATGCTAATTTTGCATTTTTGGAAAAACCCATTCCTTCCAAGCTAGTGTTTTTCA
TTGGCTCCAGGTCTAATTTTTCACTGTGGTCCCTGGCAGCCAGTCTTTTGAAGTTTAAAGATTACCTGTC
TCTTGACTGCAGTACCTTTTCTTTAATTTTTACCAAAAATATCCAGAGGTTACTGGAGTTCTTATTCAAT
ATAAGGAAAGTTTGCTGCACTTTATTACCAAGCCTCTGGGATTTTACCAGTCAAACATATTTGTGCATTA
CATTTCATTTCTTGTGAGCTAGCTGGCTGTCCATATTGAATGTTGACCCATTTGAGTACGCTAAAAGGCT
TACAGTATCAGACACGATCATGGTTTTAGATCCCATAATAAAAATGRATGTTTTTCTTATAAAAAATTAT
ACAAATGCTGAAGTGAGATTCTACTATTGTTCATTGCTTCCTTTTCTTTTTCCTTTTGCGATTTTCACTG
ATTAATAGCACATTTCTTCACAAAATTAGATAAAGTTGGTCAAAGACCAGATATTCTGGAATGGAAATTG
TAAAGCTTAATCAAAAAGAATAGCCAGTACAGCATACAATCTCAGAAACTTAGAAGCAAGTAGAAAATAA
TTGGTTGATGTAAACGAAAGTGCCATTTTAGTAAAGGCAGGAAAAAAAATAGCAATATTTGAGTTATGTAA
GGATAAAAAATCCACTGACTTGTATTTTTGCACAAGAGGCTGGTCTGAATATGATTGTTCACATTAAGAG
TGTTTATTCGTCGGTTCATTTTGGGGATTTTCCCCCTTGATGTTTTGACAGATTGAAGTGAGCTTTAGTG
AGCAAAAGGATCAGAATGCAGGGAACACTAAGCTGTGATGAAGAAAGTGTGGTAAAAAGCCAGAGTAGTT
TTATACAGACAAAACCAGTGTCAGGCCTTTGCAGTAGGCTTGAGTGAACTTCTGATCTAGATTTGAAAGT
AAATTTTATGAAGACATTGCCCATTTTTACTTCCTCATTCATTATTGTACCAGCATCATAGCTTTATTAC
TCTAATCCCAGGTAAGTCAAGCCTACAATGCCCTAGAGGAAGAGTAAAACCAGAAATTCATGCTGGCTTA
AATAATCTATTTTTGTTTCTTTTCATTTGAATATTTAAATTTTATGGTTTATTAAAAAATTAAATAAAAA
AGAAAAAAAAAAAAAAAAAAAA

FIGURE 24

GAATTCCGGGAAGCCAGACGGTTAACACAGACAAAGTGCTGCCGTGACACTCGGCCCTCCAGTGTTGCGG
AGAGGCAAGAGCAGCGACCGCGCACCTGTCCGCCCGGAGCTGGGACGCGCGCCCGGGCGGCCGGACGAAG
CGAGGAGGGACCGCCGAGGCTGCCCCCAAGTGTAACTCCAGCACTGTGAGGTTTCAGGGATTGGCAGAGG
GGACCAAGGGGAC**ATG**AAAATGGACATGGAGGATGCGGATATGACTCTGTGGACAGAGGCTGAGTTTGAA
GAGAAGTGTACATACATTGTGAACGACCACCCCTGGGATTCTGGTGCTGATGGCGGTACTTCGGTTCAGG
CGGAGGCATCCTTACCAAGGAATCTGCTTTTCAAGTATGCCACCAACAGTGAAGAGGTTATTGGAGTGAT
GAGTAAAGAATACATACCAAAGGGCACACGTTTTGGACCCCTAATAGGTGAAATCTACACCAATGACACA
GTTCCTAAGAACGCCAACAGGAAATATTTTTGGAGGATCTATTCCAGAGGGGAGCTTCACCACTTCATTG
ACGGCTTTAATGAAGAGAAAAGCAACTGGATGCGCTATGTGAATCCAGCACACTCTCCCCGGGAGCAAAA
CCTGGCTGCGTGTCAGAACGGGATGAACATCTACTTCTACACCATTAAGCCCATCCCTGCCAACCAGGAA
CTTCTTGTGTGGTATTGTCGGGACTTTGCAGAAAGGCTTCACTACCCTTATCCCGGAGAGCTGACAATGA
TGAATCTCACACAAACACAGAGCAGTCTAAAGCAACCGAGCACTGAGAAAAATGAACTCTGCCCAAAGAA
TGTCCCAAAGAGAGAGTACAGCGTGAAAGAAATCCTAAAATTGGACTCCAACCCCTCCAAAGGAAAGGAC
CTCTACCGTTCTAACATTTCACCCCTCACATCAGAAAAGGACCTCGATGACTTTAGAAGACGTGGGAGCC
CCGAAATGCCCTTCTACCCTCGGGTCGTTTACCCCATCCGGGCCCCTCTGCCAGAAGACTTTTTGAAAGC
TTCCCTGGCCTACGGGATCGAGAGACCCACGTACATCACTCGCTCCCCCATTCCATCCTCCACCACTCCA
AGCCCCTCTGCAAGAAGCAGCCCCGACCAAAGCCTCAAGAGCTCCAGCCCTCACAGCAGCCCTGGGAATA
CGGTGTCCCCTGTGGGCCCCGGCTCTCAAGAGCACCGGGACTCCTACGCTTACTTGAACGCGTCCTACGG
CACGGAAGGTTTGGGCTCCTACCCTGGCTACGCACCCCTGCCCCACCTCCCGCCAGCTTTCATCCCCTCG
TACAACGCTCACTACCCCAAGTTCCTCTTGCCCCCCTACGGCATGAATTGTAATGGCCTGAGCGCTGTGA
GCAGCATGAATGGCATCAACAACTTTGGCCTCTTCCCGAGGCTGTGCCCTGTCTACAGCAATCTCCTCGG
TGGGGGCAGCCTGCCCCACCCCATGCTCAACCCCACTTCTCTCCCGAGCTCGCTGCCCTCAGATGGAGCC
CGGAGGTTGCTCCAGCCGGAGCATCCCAGGGAGGTGCTTGTCCCGGCGCCCCACAGTGCCTTCTCCTTTA
CCGGGGCCGCCGCCAGCATGAAGGACAAGGCCTGTAGCCCCACAAGCGGGTCTCCCACGGCGGGAACAGC
CGCCACGGCAGAACATGTGGTGCAGCCCAAAGCTACCTCAGCAGCGATGGCAGCCCCCAGCAGCGACGAA
GCCATGAATCTCATTAAAAACAAAAGAAACATGACCGGCTACAAGACCCTTCCCTACCCGCTGAAGAAGC
AGAACGGCAAGATCAAGTACGAATGCAACGTTTGCGCCAAGACTTTCGGCCAGCTCTCCAATCTGAAGGT
CCACCTGAGAGTGCACAGTGGAGAACGGCCTTTCAAATGTCAGACTTGCAACAAGGGCTTTACTCAGCTC
GCCCACCTGCAGAAACACTACCTGGTACACACGGGAGAAAAGCCACATGAATGCCAGGTCTGCCACAAGA
GATTTAGCAGCACCAGCAATCTCAAGACCCACCTGCGACTCCATTCTGGAGAGAAACCATACCAATGCAA
GGTGTGCCCTGCCAAGTTCACCCAGTTTGTGCACCTGAAACTGCACAAGCGTCTGCACACCCGGGAGCGG
CCCCACAAGTGCTCCCAGTGCCACAAGAACTACATCCATCTCTGTAGCCTCAAGGTTCACCTGAAAGGGA
ACTGCGCTGCGGCCCCGGCGCCTGGGCTGCCCTTGGAAGATCTGACCCGAATCAATGAAGAAATCGAGAA
GTTTGACATCAGTGACAATGCTGACCGGCTCGAGGACGTGGAGGATGACATCAGTGTGATCTCTGTAGTG
GAGAAGGAAATTCTGGCCGTGGTCAGAAAAGAGAAAGAAGAAACTGGCCTGAAAGTGTCTTTGCAAAGAA
ACATGGGGAATGGACTCCTCTCCTCAGGGTGCAGCCTTTATGAGTCATCAGATCTACCCCTCATGAAGTT
GCCTCCCAGCAACCCACTACCTCTGGTACCTGTAAAGGTCAAACAAGAAACAGTTGAACCAATGGATCCT
TAAGATTTTCAGAAAACACTTATTT

FIGURE 25

CGCCGCCTGTGCAGCCGCTGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCTGCC
GCCCCGGCTGCCGCGCCGCGCCGCTGCCTCTGCCCCGGCCGCCCCCGCCGCCGCTGCCGCCGCCGGCCCG
CAGCCAGCCAGGCGGGCGGCCCAGCCCGCCTGAGCCCGCAGCGGCTGCCGCCGCAGCGTCGGGTCGCTGG
GTGCGCGGGCTACCGCGGACCGAGCGGACCCGAGTGGGCGACCAGGCGCTTGCCCGCCCAGTGCCACTGC
CGCCGCTTCCTCGCCGGAGCACAGGACCAGACACCTCCAGCGCCCGCTGCTGCTGCCGATGCGGCCCGGA
CACTTTTAGCTGGGCGGGAGGGCTGGAGAGCCGGGGGCCGCCGAGAACCGCCAGCGAGCTGTGCCGAGAG
CCGCGCCGACCCGCTGCGATCAGGGACAGGCGCCCGCCCGCCGCCGCCGCCTGGCCGCTATGGATCTATT
CGACTTTTTCAGAGACTGGGACTTGGAGCAGCAGTGTCACTATGAACAAGACCGTAGTGCACTTAAAAAA
AGGGAATGGGAGCGGAGGAATCAAGAAGTCCAGCAAGAAGACGATCTCTTTTCTTCAGGCTTTGATCTTT
TTGGGGAGCCATACAAGGTAGCTGAATATACAAACAAAGGTGATGCACTTGCCAACCGAGTCCAGAACAC
GCTTGGAAACTATGATGAAATGAAGAATTTGCTAACTAACCATTCTAATCAGAATCACCTAGTGGGAATT
CCAAAGAATTCTGTGCCCCAGAATCCCAACAACAAAAATGAACCAAGCTTTTTTCCAGAACAAAAGAACA
GAATAATTCCACCTCACCAGGATAATACCCATCCTTCAGCACCAATGCCTCCACCTTCTGTTGTGATACT
GAATTCAACTCTAATACACAGCAACAGAAAATCAAAACCTGAGTGGTCACGTGATAGTCATAACCCTAGC
ACTGTACTGGCAAGCCAGGCCAGTGGTCAGCCAAACAAGATGCAGACTTTGACACAGGACCAGTCTCAAG
CCAAACTGGAAGACTTCTTTGTCTACCCAGCTGAACAGCCCCAGATTGGAGAAGTTGAAGAGTCAAACCC
ATCTGCAAAGGAAGACAGTAACCCTAATTCTAGTGGAGAAGATGCTTTCAAAGAAATCTTTCAATCCAAT
TCACCGGAAGAATCTGAATTCGCCGTGCAAGCGCCTGGGTCTCCCCTAGTGGCTTCCTCTTTATTAGCTC
CTAGCAGTGGCCTTTCAGTTCAAAACTTCCCACCAGGGCTTTACTGCAAAACAAGCATGGGGCAGCAAAA
GCCAACTGCATACGTCAGACCCATGGATGGCCAGGACCAGGCACCGGACATCTCACCAACACTGAAACCT
TCAATTGAATTTGAGAACAGCTTTGGGAATCTGTCATTTGGAACACTCTTGGATGGAAAACCCAGTGCAG
CCAGTTCAAAGACTAAACTGCCAAAGTTCACCATCCTCCAAACAAGTGAAGTAAGCCTTCCCAGTGATCC
AAGCTGTGTTGAAGAAATCTTGCGGGAGATGACCCATTCCTGGCCTACTCCTCTCACTTCCATGCATACT
GCTGGACACTCTGAGCAGAGCACCTTTTCCATCCCAGGACAGGAATCGCAGCATCTGACCCCAGGATTCA
CCTTACAAAAGTGGAATGACCCAACCACCAGAGCTTCTACAAAGTCAGTGTCTTTCAAATCGATGCTTGA
GGATGACCTGAAGCTGAGCAGTGATGAAGATGACCTTGAGCCTGTGAAGACCTTGACCACTCAGTGCACT
GCCACTGAGCTCTACCAGGCTGTTGAAAAGGCAAAACCTAGGAATAATCCTGTGAACCCACCCTTGGCCA
CTCCCCAGCCCCCACCTGCAGTGCAAGCCAGCGGGGGTTCTGGCAGCTCCAGCGAATCGGAGAGCAGCTC
TGAGTCGGATTCAGACACTGAAAGTAGCACCACTGACAGCGAATCTAATGAGGCACCTCGTGTGGCAACT
CCAGAGCCTGAGCCACCCTCAACCAACAAGTGGCAACTGGATAAATGGCTTAACAAAGTGACATCCCAGA
ACAAGTCTTTTATTTGTGGCCCAAATGAAACACCCATGGAGACTATTTCTCTGCCTCCTCCAATCATCCA
ACCAATGGAAGTCCAGATGAAAGTGAAGACGAATGCCAGTCAGGTCCCAGCTGAACCCAAAGAAAGGCCT
CTCCTCAGTCTCATTAGGGAGAAAGCCCGTCCACGGCCCACTCAGAAAATTCCAGAAACAAAGGCTTTGA
AGCATAAGTTGTCAACAACTAGTGAGACAGTGTCTCAAAGGACAATTGGAAAAAACAGCCCAAAAAAGT
TGAGAAGAACACCAGCACTGACGAGTTTACCTGGCCCAAACCAAATATTACCAGCAGCACTCCCAAAGAA
AAAGAAAGTGTGGAGCTTCATGACCCACCAAGAGGCCGCAACAAAGCCACTGCCCACAAACCAGCCCCTA
GGAAAGAACCAAGACCTAACATCCCTTTGGCTCCCGAGAAGAAGAAGTACAGAGGGCCTGGCAAGATTGT
GCCAAAGTCTCGGGAATTCATTGAAACAGATTCATCTACATCTGACTCCAACACAGATCAGGAAGAGACC
CTGCAAATCAAAGTCCTGCCTCCGTGCATTATTTCTGGAGGTAATACTGCCAAATCCAAGGAAATCTGTG
GTGCCAGCCTGACCCTCAGCACCTTAATGAGTAGCAGTGGCAGCAACAACAACTTATCCATCAGTAATGA
AGAGCCAACATTTTCACCTATTCCTGTCATGCAAACTGAAATCCTGTCCCCTCTGCGAGATCATGAGAAC
CTGAAAAACCTCTGGGTGAAGATTGACCTTGACTTACTCTCTAGAGTACCTGGCCACAGCTCACTCCATG
CAGCACCTGCCAAGCCAGACCACAAGGAGACTGCCACAAAACCCAAGCGTCAGACAGCTGTCACAGCTGT
GGAGAAACCAGCCCCTAAGGGCAAACGTAAGCACAAGCCAATAGAAGTTGCAGAGAAGATCCCTGAGAAG
AAGCAGCGCCTGGAGGAGGCCACAACTATCTGCTTGCTCCCTCCTTGCATCTCACCAGCCCCACCCCACA
AGCCTCCCAACACTAGAGAAAATAATTCATCCAGGAGAGCAAATAGAAGAAAGGAAGAAAAACTATTTCC
TCCTCCACTTTCCCCACTGCCAGAGGACCCTCCACGCCGCAGAAATGTCAGTGGCAATAATGGTCCCTTT
GGTCAAGACAAAAACATCGCCATGACTGGACAAATCACATCTACCAAACCTAAGAGAACTGAAGGCAAAT
TCTGTGCTACTTTCAAAGGATATCGGTAAATGAGGGAGACACTCCAAAAAAGGCATCCTCTGCCACCAT
CACTGTCACCAATACTGCTATTGCCACTGCTACTGTCACTGCTACTGCCATTGTCACCACCACTGTCACA

FIGURE 26.1

GCTACTGCCACCGCCACGGCCACCACCACAACTACTACCACTACCATTTCCACCATCACCTCTACCATCA
CTACTGGCCTCATGGATAGCAGTCACCTGGAGATGACGTCCTGGGCGGCTCTGCCCCTTCTATCCAGCAG
CAGCACTAATGTCCGGAGACCCAAGCTCACTTTTGATGACTCGGTTCACAATGCTGATTATTACATGCAA
GAAGCTAAGAAGCTGAAGCACAAAGCTGATGCACTGTTCGAGAAATTTGGCAAAGCTGTGAATTATGCTG
ATGCCGCCCTCTCCTTCACTGAATGTGGCAATGCCATGGAACGCGACCCTCTGGAAGCAAAGTCCCCATA
CACCATGTACTCTGAGACTGTGGAGCTCCTCAGGTATGCAATGAGGCTGAAGAACTTTGCAAGTCCCTTG
GCTTCGGATGGGGACAAAAAGCTAGCAGTACTATGCTACCGATGTTTATCACTCCTCTATTTGAGAATGT
TTAAGCTGAAGAAGGACCATGCTATGAAGTACTCCAGATCACTGATGGAATATTTTAAGCAAAATGCTTC
AAAAGTCGCACAGATACCCTCTCCATGGGTAAGCAATGGAAAGAACACTCCATCCCCAGTGTCTCTCAAC
AACGTCTCCCCCATCAACGCAATGGGGAACTGTAACAATGGCCCAGTCACCATTCCCCAGCGCATTCACC
ACATGGCTGCCAGCCACGTCAACATCACTAGCAATGTGTTACGGGGCTATGAACACTGGGATATGGCCGA
CAAACTGACAAGAGAAAACAAAGAATTCTTTGGTGATCTGGACACGCTGATGGGGCCTCTGACCCAGCAC
AGCAGCATGACCAATCTTGTCCGCTACGTTCGCCAAGGACTGTGTTGGCTGCGCATCGATGCCCACTTGT
TG**TAG**TGGGTGTTCTCAGATCTCTAGCATCACGACCCATCACTCTACCTCTACCAGCGCACTGATGGTCA
CTGGTGGAACTCCACTCACTGGGGAACGTTCTCTTTGGTTATGTTTGTTTTTATGCTTCTTTTGTTATCT
GTAAAAAACAGAAGTCATTGTAAGTTGACACTACAACTTAAGGGCAGTGTACGTTTTATTACTTAGTCAT
TTTTTTTCTTTTAGCATTTGATATGCATTTCTCAGATTCCACCATCTTTTTGTGCTTTATGGAATGACAG
TCCCTACAATATTGTTTTAAGCCCACACTACCCAAAACAAAGAATGGGAAGCACTTGTGATAAAGACAGG
CTCCTGAGAAATGCAACAAGTGGTCTTACATATACATGAGAACTTAGACACAAGGGACCATCCCCCAAAC
TCTACTCTTATACCCAGAAAAGAACATATTTCAGAATCTGTCAAACTTTTGTGTATCCCACAGATTCAAT
CTTCAGGTGAGAATTTTCATTGTCAAAACCCACTGGTTAGATGTTGTAGCAACATCATAAAATCAAGAGT
ATCAAGAAAATAAATGAGCATAGCAATGCTACTCTTAAAAAGATGCTATGCCACACAACCAGAGGACTTT
CTTGTTAGCATCCCTTTCCTGATTCCCTATTTTGTTAATTTTAATGATAAGAAGAAAGGGTGACATTTAT
TTTGACAAGTTTTAGGCATCAGCTGGCATCAGTGTTTTTCAACTCCATTATTTGAAGTGTAAATCCTCAC
CTGGGGTTCTCTGTGTGCAAAGCTGTCCTTTTGAAGAACAGTTTGGTTGATGCATGCCTTAGTAGCCAAA
ATGCTACACTCTAGACTTACAAGTGGGAGTTAAGAGAGGTCTGGAAAGTGTCCAACAAGGAATTCACACC
TCTGCCTCCTTTGCAACAACAACATTTACACAGTTGGTAAGTGGGTCCATAACTGGCAGGATTTTTAAAT
TGTATTTTGCTCAAATCTATGGGAACAAAAGTCAAGGTATCACTACCTAGAAGTAATGATATACAGTTTT
CTTCCTAGTGGCTTGAAAATCTGGACTTCCTCAATTATTATTCACATTTTCTCTCTTATAGGTTTTCTGT
TTTCTACTTTCTTTTTTCTCTTATCTGTGTTTCCCTTTCCTTTGTTTGGCTCATTAACTTTTGACTGAAT
TACAATTACTCCTTTTATTAAAGTCCATATTATTGTGAATCATTTCCATGAAAATTTCTAAGAAAACTCC
AAACTCTCTAAATAGTAGCTAACTTTTATTTTTTTAAAATGAGTCGTGGGGTAGTGCTTCACCTTGAGAT
GCTTTGAAAGAGCCCTAAACATTGGGAACCATTCACCTAATTTGGAGACATTTCTCACTGGTTGTGACTA
CCCCCTTATGATCCTTCACATTCATTTTATGTCCCTAAACATCACAATGTAAATATCATTTTTGATGTTC
CAGCTCACCAGAAGATTCTTACACTTGGGGTAAACACTATCCATGCATTACTTACTGGTAATTACCTGCT
GGTATATAATTCCATGTAGCCTTTAATATGCTGGGTTATCAAATTCTGTTCACTGAGTTATGACCAGATA
AATAATAGATATGCACATGAAAGATGCAAACTTGTGTGATTATTAAAGCCAGCCATGCAGGTCCATGATA
GAAACAGCAGGTGATGACTCTGCACTCTCATTGTCAAGGTTAGCTATATCCCCAGTTGCAAAACAGCCAG
ACTTGAGCTGTGCTCTGGTCATCTTTGAGTTTAAGGCCTTTTGTTGTATAAGGCTGTGGAAGTTGTACTC
CAATGGCTGAAGCCATGTTGTTAATATGGCTGATGGGAGCATCCCTGCAGCTGAACCCAGCACTTTTTAT
GCTCCCACTGTGGTTGAGCTTTATGTTTACAGTCTCAGCAACAACACTTATGCATCCAAACACTCACAAA
TGAAACCTGAAAGAATCTTTTCTGAGCCTCTTAAAAGAGGAAAATGATGATAACATTAAAGACTCTGAAC
ACCCAAGGTTGGTGTCACATATAAAAATTAAGCTGATGACTTTGCAGTGACTCAAGTTGTCTCTTTATCA
TGGTTTACCAGGTAGAGTGCCTGGCTATTACTATATAATGAAGCCCACTGGCTTGACTTGTAAGTTCAAC
CTAAACCACAATCCTAGACCATCATGGATTTAGGAGTAGATTCTTCTTGAAATCCCACATCCAGAAACTA
GACATTAGAATGTTGAGGCAGTTTCCCAGAGAAACAAGCATATTGCCTCATGGATGAAAGACTTGTAGTT
CTAGTTTCAGTGACTTGTTATATCTACTTACATACAACAGGGAGGCAAGAGGATTCTCTGTCATCTCTGG
TGACTGAGTGTAAAATATGTGCCAAGTCTGCAGCACAGTGACCAAATCTGACAATCGAGCTCTGGATCAC
CACTTGATTATGTAGTAGACTCATTTATAAAGCAGCTTAGGAACTAATTAAACATGGAGGATGAATTACC
TTCCTATCCCTTGAGATAAGACATCTTTCAGTTTCATGATTAAGGATTGTTGCTGTTTTATAGTTACTCT
GTTCATCACAGTGTAAATGGTGATGCGTGTCGTAGGTGTGCAGCTATTTGAGGGACTAAGGATGGAGAT
ATTCTGTCAAATGAATCTCTTCAGTATACCAGTTTGTGGGAGGGATATGAGACATGTGGATGGCAGTGAG

FIGURE 26.2

AGATCGTGCCTCTAGATCTTGATGGAGGCTTGGTGAGACACACTTAAATAAGCACGTGGAGGTTAGAATA
GAGGGCAGAGTAAAAGGAAGCTCCATCTGAGCAAGTACACCAAATGATCTCAGCCCTGCAACTTGACCCA
GGTAGGGCCACCACTACGCCTTCACTTGTCACCCAAGCTCCAACCACAGAGAGTTTGACAAGTTTGTGTT
ATGATGTTGGCTTGGCTTTGTATTTTTAATTAACTTTGGATTTTTAGTGGTTTTGTCATATAACTGTCTG
AGTTTGGTAGGTAGGATTACTTTGAAAAGGGTTTACTAGTGTGGTCCTCCGGGTAGAATTTAGCTGTAAC
ATGTTGTTAGCCAGCCTGTAGACTGTTAATTACTTAATAATCTCATTGGGAAAATACTAGTAGTTTTATA
TTTGGATGACATAATTGGAAAAAGCAGATTAGCTGCTACTACTTTTAAAAGACTTAAGGTCGGGATGCCT
TTTTTTCCATGTAAGGAAATGAAAAGACCCAAAATCTTCAGGCAAAAAGCAAGTTGCAAAATTAGAAACC
ATTGGCTAAAAATGTGTTTTGTTGAGTTTCCAAATGGATGAATTTTCATTTGGACATTACATCACTAAAT
TCATTAGATTTTGTCTGCATTGGAAAGATACTCTTCTAGCATATCTTTCCCAAAGATATCTAATTTGGAT
TCTGTTTCATGCAAATTTGCATCCCGGAGGTTGAAGTTGGAGTTTGAGGTTGGAAAATATCTTTGAAGGC
AGAATCAGTTGAGTTGTGAGGGTGAAGCCTCACATACTTCTCAACAGACATGATAAAATTCACCTGCATG
AGTTGGCAGGTGGGAGAACCAAACTGGATCACTGGGTAAGACTACTCAGTAAAGCAATGAACTGCTTGCT
TAGAGAAGCATCACTATCCCCATTGAGAAAAATGTGTGGCAAGATGATACAGCTACACAGTATCAAATGA
ATGGGTCAATTCAGCACCCCCAAATTTAATTCTGTGGGGAAAAATTATTGAGCCAGTTGTCAGTGTTCTG
TTACATGACTGGCAGACTAAATTCTTCATCGTTGTTGTTATTGTTGTTGTTGTTTCTCATTTTCACTCGC
ACGGCCTTATTCTCATAATTAAAATCTAATTCATTTTCTCTTTAGTGTTAGTAGACTCCAACAACAGAAG
TGGCATCTGTGTATTCATAATCAGCATTTACCCTGGCAGGAGACTAATCAGATAGGCCGGTCTCAGACAT
TAATCCTACCATCTGATATTTTTGGTGAAGGAAAAAGTATTAATTCTCTTTCCATCCTCCTCCTCAGAAA
TATAGAAGCCCTCTTTACCAAAATCATCACATTTTACTCTGTAATCTACCAGCTAAAAGAAAATTGCATT
GAAGCCCCACAAAGCCAGATTGCAGTTCTTGCCCCTTTTTGCGTCTGACATGAGATGTTAAAGAATTATT
CATTGTGCTCACATTGGGTTAGGGGACACTGAACTGCTTTTTAGATCCATGATCAGTCATCATTCTTCTA
AGAGATTGGAGCTTTGCTGTTTCATTAACTGTGCAGTGTAGACTAATGGTGTTTAATAAAAATCATTCAA
AATTTCAAACTCTTTTGCCAGTGACCTCAATTTTGTTGGCTCTGTGATTTGTATCAGACTTTGAGGAGGG
AAGGGGGAAGTGAAGGAAGCCTACGTCCAGGCCCCTGACAGGATGCTGCAGTAGCAAGCTCAAGCTCGCC
TGCCTGCCAGCAGTTGCTGGTGAGCAGCAGCATGCAGACCAGCTGTGGGAAGCCTCCTGAAGAATGCCCC
AGCTGATGCTTTCAGCTGGGAATAGTTTGTTCCTATTGGGGAACTCATTGTTCTCCAGTCTCTGCAGCAG
GAAGCCAGCTGTCATATTCGGAGGGAATTTCAGATGCTTTACCTTTTTGGTTTTGTCCTGCATCACTCAT
GTGGCTACGAAAGTGTCTCTGAGAATAGAGCCCAATGTGGTGACAATGGGTAGTCAAATGCACCCCAGAT
GCTCAAGCCCTGTTGTGGTTCTGCAGTGTTTATGAAATTGGGAGGAAGGAGACCCTGGACAGTAAGCAAA
ATTGGAGACACTCCAACGAGGCTAAGTTAATGCCGTGTTGCCCAGAACAAGATCTAGCTTCTCATTTGGT
CAGCCTAGCATGCAACCAGTGGTGTGCTGGTAAAATGTTTAACAACCAGCTCGCTGAGAATAGAAAGCAC
CTGGTTTGCACCATTTGCCAATTTCCATGGCATAAATACTACCACTTTAGATGATTTTAAGCTACCAACT
GTGATGTCACTGAACACATGGTTGGAAAGAGATGCACGCAGTTGGCTCTTGCAAGCCTGGGCAAAAATGC
TTCAACACGCCACTGGATGCAGCCAGTCAGAGGGTTCATATTTAATATATGTGTTCATGTGGACACACAC
AGACACACACACACAAACTCACCCTTACACACACACTTCGATGACTAAAACAATTACATAGTTTTAAGAT
ATGAATCAATGTGTGAATGTAGAAAGCTTATGATAAGGCCCTAGAGGTATGGGTTGCCCTGGAAGCCTAG
GTTTTAAGCAGGAGAATAGCTGAGAAGAATGAAGCCCTCCTGAGCTGAAAGGAGAGATGGATCAATGGAG
ATGGTTCCATCATCTCCTTCCATATCTCACAGGTAAAATGGGCACTCAGAAAACCCTCACGATTGATTTT
TTAAAAAGATAAGTGAGTGTTTTTTATTTTATTATTATTGTCATCATTATTTTGATTTACAAATGCTATT
TGTAACTTTTACATGTAACTAGGATAAAGTATTTACGGGAACTCTATGGAGAATAGCACAATCCAGAATT
TACTGTGTTTTTCTTTTATGTGACGTGGAAACTCAGTAATTCTCCCACCTTCACATTGTTGTTCATAAGA
ATTTTACTTTAGTTATTAGGGAATCTAAGTTTTTTGTTAACATTTGTTTTTAGTTAAAAGTATCTACTTA
CTGTTTTAGCTCTGAACTCAAACCAGAATATCTCTGTATCAATTGCATGACTATTCAGAAACAATAATCC
AAACCAAAATAATTCTTTTTCCACCCAGTACGAAGAAAACTAAGCTCAGTAACAAGAAGGCATAAACTAA
AGTATATAATGAGGCTTTCATTAAATACACACACACACACACTCACACACACACACATACACTTTTTAAA
TTTTTAAATTAGGCCTCCACACATAAATCATTTTGAAAGTAGAATAGAAAATCTCAAAGAATTCATTCTC
CTGGTCCTGTGCATCTTCTGCAGTTAATAAGAGGTTTGTATCTGGAAAGATGGAAGAACTTGTTCTAAAA
TCTTATTTTTCAAAAAAAAATTTCCATTTTCTCTCTGGGCCTGTATCCATGGTTGAATGTTAGCCCTGGA
GGAGATCCATGTCTTACTCGCTCTTTCTGGCCCTTCTGTCTTTTGCCTCTGCAATTCTTTTTGTAGCTGG
CACGATAGCAGGGACTGGGGGTCTATCCTTTCATGGTATTGCTACAATATTTGTCCTTACTGGAAAATGG
TAACATCCGGGTCTGATTTAATTGGCATTACACTTACACAGGGACTCTGAGCACCCCCGTCACCACACCA

FIGURE 26.3

GACAGTGGACCAGTTTTCACAGCTACAAAGAGCTAGAAATGTGTTTAACATCATCCAGTGCATCCCCTAA
TTCAAAACCATCCTCACTAATCAATCATATTCACCCATAAATATTACAAATGAGATTGATTCCATCTCAA
GACAATTTGTCAAATACTTAATTTTCTTCCTGGATGATTCTACTTACTGGATATTTTAGAAAGAGAAATG
TCTGAGATAAAATCCCTCACATTTACTCAATATAACAAATTACTGTTTCTACTCCTATTCTGAGTAGTGC
TTCTGAAGATTGTTTGCTGTAGTGTTGTCTTTGATAAAATGAATGTCAGTAGTGAGCCTTTTAGAGATAC
CATGCTCAGACATCCTCTTTGGGATCAGAAGATACCTAAAATTCTCCCCTTTTGCCCACTTGGTTAGATG
AGTGATATATTCTTTGGATCCTGCAAAGAAGAGATTGGTTTCTTTTCTTTTCTGGTGGTGGTAGTGGTTG
TATCTGTGGCTGTGATGGTTGTTGTTACTTGTCTCTCTCTCTCTCTGGCTCTGGCTTTTGCTTTCCTGCT
AGTGTTCTTTCTCTTTCCAAACAAATAGTTAAATTAAACGTGAGCTTCTGAATTGTACTTGTTCATACTT
TCAAAACATAACAGATTAATAAAAATAGATGTGTCCTGATTTAAAACATGCCCCCTGGAAAGGCATGCTG
TATTATGAAATCGTGATAATATAACTGCATTATTACATGGCAGTATAAATATTAGTCTGTTGAATTCATT
TGTCCAATTGTATAACTTTGTGGAGCAGTGTTTTGACCTTTGATACATAATTCTGGAGCAAGTGGAGTGG
TTGCAGGCAGATGAGACAGTGTTATATCAGGATTTTTCAATCAACTTTAGTTGGAGGCCTGGCAATTACA
AACATCTTCAGATGTTTCTGTAACCATTATAAATATGAAAAAAACCTCTTCAAAAAATTTCCCATAGTAC
TTCAGTCAAGACTTTTTAGGTTTATCTTTTTTTTTCATTTCTCCTTTTCCTTTTCCATTATTTTTCGAT
GGGGGGGTTGTTATCATTGACTGAAGAAATATTTTGATTGCAATGGTCTCTCTCTCTCTCCCCCTCTCTC
TCTCTCTCCTCTATTCTTTCCTCCTTCCCTCTGTCCATCACCCCTCATTAAAATATTGAAATCTGGAGTC
TTTGATAAATCTGCATTAGACCAGGCTATATGCTAGGAATGAAATCTGGGCAAATATCGATGGGTTTTCA
AAGAATGCTCCATGTTCATTGGGCCCTTTCACACCCCACAGTGATAAATGAAAAGGATAGAGGTAGTTTT
TTCAAAAGAGCACTTTAATAATATCCTCTGAGACCTAATGCAGTTTAACAAATGACTCCACCTATTTTTC
CAGTAGGTAAATTGACTGAGACTTGCAAAATACCCCTGAGAGTTGTCAGGGGTGTCTTCTGCCTGGTCTA
TAGCGTGTGTGTTTGCTTTGTATCTAACAGGCACATTCACGTCTCGTGTACTCATATGAAGTATTTCCTA
ACATTCCCATTAGCCTGTATATAAGAATCAGAAAGATAATCCCAACATGTTGTAAATGAAGATGTGACTC
TATAACCTTTCTCTTCTTCCTGGAAAAAAAAGGACATTTTCATGCATATTTTAAACAGAAATTTTGTATA
TTTAAGTGTCATAGAAAATATTTATTGAGTAACTGGGACACAAATGGGAATTTAATTGTCATCATATGCT
TTGTGTGTGGGGATGCTTACCAACACCATGTCGCTGGACCATTGTGGCAAGCCATAACTGCACAAAGAGT
ACACATCGTCAGTGTGTGTGTGTGTGTGTGTGTGCGCGCACGCACGTGCGTGTGTGTGTCCCTGCATGTG
CAACATGTCTAGCTTGCTGTCCTTCATGGGATTTTAGCTTTCCCTTCTTGAAAAACATTATTTTACAGTT
CCAGGAGGCCCTGGTTACATTACTATATGAAGGCAGTGATTTGAAATGAAAATTCCTTTCCTCTTGGAAG
CTTTGGTCATAATATCATGGTTCAATTAAACGGATTCCACCGGACTTTGTGATGAAAAAGGCTCTGTTAA
AATCCAATTGAGTTTCCAAGAGGAAATTGTAGTAGGTCAAGATGCATGAGAGGGAAGATGGAGGCCACCT
CAGCTGGAGAACATGAGCTGAGTTGAGCCCTCAGTGTTGAAGTTGACTTGCTCCAAGCTGCAGTCTAAAA
CCCTGGGGCCCGTGCCTGGCCTATGCTCCCTCCCAAGTAAGTAGAGGAGCAGAACCATCAGGAACAGCCT
GCCTGGCTCCTATGAAGAAAACTTCCTGACGTCCTGTCCCCAAAGGAAGACCCTTTCCCCAAGGGCACCC
CAGGTGGCCATTAAATTGTGATGATCATTCAGAAAGTGCCCCCTTGGCTTTATGAGAATCCAATTAGTCT
TCTGAACCACCTTTTCTTGGGTGCAGATTTCCAACATTCATGCTCATTGCAGATCCACCAACTGTCACTG
TTCTTAACAAGCATGCTCGTCTTGTCAGAATTTCAGTAAGTTCCAATTTCCTGTACAGACCAGGGTAAAC
TGTTCTAAAATCAATCAATTAATGAAATGTTATCTGGTTTTTAAAAGCTGGTTTCATGTGCTTTATGTGT
ATAAAACTATATCTGCCTGTGTGGCTTTGCATTTCAAATGTGTGGCGCACAAGCGTTTTGTTGGTGCTTT
GTTCTCAGTACAGTAACTCTGTGTACAAACATTTTAATGTGGTTTTGTTGTTTTCCAACAAGATGTCTCT
GTAAAAATGATATTGGCTGAGCTGGTGCGTTGGTTTCTCTCATAGAGGCATTAACTATACTGCCAATGCA
TTGAATTATTTAAAAATGCAAAATAAAATTTTTATGAAAATCTCA

FIGURE 26.4

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Declaration and Power of Attorney for Patent Application
Déclaration et Pouvoirs pour Demande de Brevet
French Language Declaration

En tant l'inventeur nommé ci-après, je déclare par le présent acte que :

Mon domicile, mon adresse postale et ma nationalité sont ceux figurant ci-dessous à côté de mon nom.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

et dont la description est fournie ci-joint à moins

☐ ci-joint

☐ a été déposée le

sous le numéro de demande des Etats-Unis ou le numéro de demande international PCT

et modifiée le

(le cas échéant).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait références ci-dessus.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

As a below named inventor, I hereby declare that :

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed an for which a patent is sought on the invention entitled

Nucleic sequence and deduced protein sequence family with human endogenous retroviral motifs, and their uses

the specification of which :

☐ is attached hereto.

☒ was filed on

as United States Application Number or PCT International Application Number.
PCT/FR99/01513 filed on **June 23, 1999**

and was amended on

(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations,§ 1.56.

French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign application(s)
Demande(s) de brevet antérieure(s) dans un autre pays.

(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	Priority claimed / Droit de priorité revendiqué	
			☒ Yes Oui	☐ No Non
98 07920	**FRANCE**	**23.06.1998**		
(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	☐ Yes Oui	☐ No Non

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (N° de demande) (Filing Date) (Date de dépôt)

(Application No.) (N° de demande) (Filing Date) (Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365© du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande :

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.) (N° de demande) (Filing Date) (Date de dépôt) (Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)

(Application No.) (N° de demande) (Filing Date) (Date de dépôt) (Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)

Je déclare que par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique ;et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la section 1001 du Titre 18 du Code de Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hebery declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

French Language Declaration

POUVOIRS : En tant que l'inventeur cité, je désigne par la présente l'(les) avocats(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marquees : (mentionner le nom et le numéro d'enregistrement).

POWER OF ATTORNEY : As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to persecute this application and transact all bussiness in the Patent and Trademark Office connected therewith : (list name and registration number)

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(Suppply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

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Signature de l'inventeur Date	Fourth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du cinquième co-inventeur, le cas echeant	Full name of fifth joint inventor, if any
Signature de l'inventeur Date	Fifth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du sixième co-inventeur, le cas echeant	Full name of sixth joint inventor, if any
Signature de l'inventeur Date	Sixth inventor's signature Date
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(Fournier les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

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<212> ADN
<213> Homo sapiens

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<212> ADN
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<212> ADN
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<212> ADN
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<400> 18

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<213> Homo sapiens

<220>
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caa caa gtt ctt aaa aca tta caa gga acc tat ccc tga gaa gag gga    96
Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro     Glu Glu Gly
             20                  25                      30

aaa gaa cta ttc cac cct tgt gac atg gta tta gtc aag tcc ctt ccc   144
Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
         35                  40                  45

tct aat tcc cca tcc cta gat aca tcc tgg gaa gga ccc tac cca gtc   192
Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
     50                  55                  60

att tta tct acc cca act gcg gtt aaa gtg gct gga gtg gag tct tgg   240
Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
 65                  70                  75                  80

ata cat cac act tga gtc aaa tcc tgg ata ctg cca aag gaa cct gaa   288
Ile His His Thr     Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
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aat cca gga gac aac gct agc tat tcc tgt gaa cct cta gag gat ttg   336
Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
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cgc ctg ctc ttc aaa caa caa cca gga gga aag taa cta aaa tca taa   384
Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys     Leu Lys Ser
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atc ccc atg gcc ctc cct tat cat att ttt ctc ttt act gtt ctt tta   432
Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
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ccc tct ttc act ctc act gca ccc cct cca tgc cgc tgt atg acc agt   480
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145                 150                 155                 160
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                165                 170                 175

att gat gcc cca tcg tat agg agt ctt tct aag gga acc ccc acc ttc     576
Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
            180                 185                 190

act gcc cac acc cat atg ccc cgc aac tgc tat cac tct gcc act ctt     624
Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
        195                 200                 205

tgc atg cat gca aat act cat tat tgg aca gga aaa atg att aat cct     672
Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
    210                 215                 220

agt tgt cct gga gga ctt gga gtc act gtc tgt tgg act tac ttc acc     720
Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
225                 230                 235                 240

caa act ggt atg tct gat ggg ggt gga gtt caa gat cag gca aga gaa     768
Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
                245                 250                 255

aaa cat gta aaa gaa gta atc tcc caa ctc acc cgg gta cat ggc acc     816
Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
            260                 265                 270

tct agc ccc tac aaa gga cta gat ctc tca aaa cta cat gaa acc ctc     864
Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
        275                 280                 285

cgt acc cat act cgc ctg gta agc cta ttt aat acc acc ctc act ggg     912
Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
    290                 295                 300

ctc cat gag gtc tcg gcc caa aac cct act aac tgt tgg ata tgc ctc     960
Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
305                 310                 315                 320

ccc ctg aac ttc agg cca tat gtt tca atc cct gta cct gaa caa tgg     1008
Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
                325                 330                 335

aac aac ttc agc aca gaa ata aac acc act tcc gtt tta gta gga cct     1056
Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
            340                 345                 350

ctt gtt tcc aat ctg gaa ata acc cat acc tca aac ctc acc tgt gta     1104
Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
        355                 360                 365

aaa ttt agc aat act aca tac aca acc aac tcc caa tgc atc agg tgg     1152
Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
    370                 375                 380
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gta act cct ccc aca caa ata gtc tgc cta ccc tca gga ata ttt ttt   1200
Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
385                 390                 395                 400

gtc tgt ggt acc tca gcc tat cgt tgt ttg aat ggc tct tca gaa tct   1248
Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
                405                 410                 415

atg tgc ttc ctc tca ttc tta gtg ccc cct atg acc atc tac act gaa   1296
Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
            420                 425                 430

caa gat tta tac agt tat gtc ata tct aag ccc cgc aac aaa aga gta   1344
Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
        435                 440                 445

ccc att ctt cct ttt gtt ata gga gca gga gtg cta ggt gca cta ggt   1392
Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
    450                 455                 460

act ggc att ggc ggt atc aca acc tct act cag ttc tac tac aaa cta   1440
Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
465                 470                 475                 480

tct caa gaa cta aat ggg gac atg gaa cgg gtc gcc gac tcc ctg gtc   1488
Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
                485                 490                 495

acc ttg caa gat caa ctt aac tcc cta gca gca gta gtc ctt caa aat   1536
Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
            500                 505                 510

cga aga gct tta gac ttg cta acc gct gaa aga ggg gga acc tgt tta   1584
Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
        515                 520                 525

ttt tta ggg gaa gaa tgc tgt tat tat gtt aat caa tcc gga atc gtc   1632
Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
    530                 535                 540

act gag aaa gtt aaa gaa att cga gat cga ata caa cgt aga gca gag   1680
Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
545                 550                 555                 560

gag ctt cga aac act gga ccc tgg ggc ctc ctc agc caa tgg atg ccc   1728
Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
                565                 570                 575

tgg att ctc ccc ttc tta gga cct cta gca gct ata ata ttg cta ctc   1776
Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
            580                 585                 590

ctc ttt gga ccc tgt atc ttt aac ctc ctt gtt aac ttt gtc tct tcc   1824
Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
        595                 600                 605
```

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aga atc gaa gct gta aaa cta caa atg gag ccc aag atg cag tcc aag     1872
Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
    610                 615                 620

act aag atc tac cgc aga ccc ctg gac cgg cct gct agc cca cga tct     1920
Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
625                 630                 635                 640

gat gtt aat gac atc aaa ggc acc cct cct gag gaa atc tca gct gca     1968
Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
                645                 650                 655

caa cct cta cta cgc ccc aat tca gca gga agc agt tag agc ggt cgt     2016
Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser     Ser Gly Arg
            660                 665                     670

cgg cca acc tcc cca aca gca ctt agg ttt tcc tgt tga                 2055
Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys
        675                 680                 685


<210> 23
<211> 28
<212> PRT
<213> Homo sapiens

<400> 23
Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
  1               5                  10                  15

Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro
            20                  25


<210> 24
<211> 55
<212> PRT
<213> Homo sapiens

<400> 24
Glu Glu Gly Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys
  1               5                  10                  15

Ser Leu Pro Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro
            20                  25                  30

Tyr Pro Val Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val
        35                  40                  45

Glu Ser Trp Ile His His Thr
    50                  55


<210> 25
<211> 38
<212> PRT
<213> Homo sapiens
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<400> 25
Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu Asn Pro Gly Asp Asn
  1               5                  10                  15

Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu Arg Leu Leu Phe Lys
             20                  25                  30

Gln Gln Pro Gly Gly Lys
         35


<210> 26
<211> 540
<212> PRT
<213> Homo sapiens

<400> 26
Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
  1               5                  10                  15

Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
             20                  25                  30

Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
         35                  40                  45

Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
     50                  55                  60

Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
 65                  70                  75                      80

Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
                 85                  90                  95

Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
            100                 105                 110

Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
        115                 120                 125

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
    130                 135                 140

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
145                 150                 155                     160

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
                165                 170                 175

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
            180                 185                 190

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
        195                 200                 205

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
    210                 215                 220
```

```
Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
225                 230                 235                 240

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
                245                 250                 255

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
            260                 265                 270

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
        275                 280                 285

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
    290                 295                 300

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
305                 310                 315                 320

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
                325                 330                 335

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
            340                 345                 350

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
        355                 360                 365

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
    370                 375                 380

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
385                 390                 395                 400

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
                405                 410                 415

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
            420                 425                 430

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
        435                 440                 445

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
    450                 455                 460

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
465                 470                 475                 480

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
                485                 490                 495

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
            500                 505                 510

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
        515                 520                 525
```

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser
530 535 540

<210> 27
<211> 15
<212> PRT
<213> Homo sapiens

<400> 27
Ser Gly Arg Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys
1 5 10 15

<210> 28
<211> 1080
<212> ADN
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1080)

<400> 28
acc tct ttt gta gaa aag gca aat gga gtg aag tgc cat aag tac aaa 48
Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
1 5 10 15

ctt tct ttt cat taa gag aca act cac aat tat gta aaa agt gtg att 96
Leu Ser Phe His Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
20 25 30

tat gcc cta cag gaa gcc ttc aga gtc tac ctc cct atc cca gca tcc 144
Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
35 40 45

ccg act cct tcc cca act aat aag gac ccc cct tca acc caa atg gtc 192
Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
50 55 60

caa aag gag ata gac aaa agg gta aac agt gaa cca aag agt gcc aat 240
Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
65 70 75 80

att ccc caa tta tga ccc ctc caa gca gtg gga gga aga gaa ttc ggc 288
Ile Pro Gln Leu Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
85 90 95

cca gcc aga gtg cat gtg cct ttt tct ctc cca gac tta aag caa ata 336
Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
100 105 110

aaa aca gac tta ggt aaa ttc tca gat aac cct gat ggc tat att gat 384
Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
115 120 125

```
gtt tta caa ggg tta gga caa ttc ttt gat ctg aca tgg aga gat ata     432
Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile
    130                 135                 140

atg tca ctg cta aat cag aca cta acc cca aat gag aga agt gcc acc     480
Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr
145                 150                 155                 160

ata act gca gcc tga gag ttt ggc gat ctc tgg tat ctc agt cag gtc     528
Ile Thr Ala Ala     Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val
                165                 170                 175

aat gat agg atg aca aca gag gaa aga gaa tga ttc ccc aca ggc cag     576
Asn Asp Arg Met Thr Thr Glu Glu Arg Glu     Phe Pro Thr Gly Gln
            180                 185                 190

cag gca gtt ccc agt cta gac cct cat tgg gac aca gaa tca gaa cat     624
Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu His
        195                 200                 205

gga gat tgg tgc tgc aga cat ttg cta act tgt gtg cta gaa gga cta     672
Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu
    210                 215                 220

agg aaa act agg aag aag tct atg aat tac tca atg atg tcc acc ata     720
Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile
225                 230                 235                 240

aca cag gga agg gaa gaa aat cct act gcc ttt ctg gag aga cta agg     768
Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg
                245                 250                 255

gag gca ttg agg aag cgt gcc tct ctg tca cct gac tct tct gaa ggc     816
Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly
            260                 265                 270

caa cta atc tta aag cgt aag ttt atc act cag tca gct gca gac att     864
Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile
        275                 280                 285

aga aaa aaa ctt caa aag tct gcc gta ggc ccg gag caa aac tta gaa     912
Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu
    290                 295                 300

acc cta ttg aac ttg gca acc tcg gtt ttt tat aat aga gat cag gag     960
Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu
305                 310                 315                 320

gag cag gcg gaa cag gac aaa cgg gat taa aaa aaa ggc cac cgc ttt     1008
Glu Gln Ala Glu Gln Asp Lys Arg Asp     Lys Lys Gly His Arg Phe
                325                 330                 335

agt cat gac cct cag gca agt gga ctt tgg agg ctc tgg aaa agg gaa     1056
Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg Glu
            340                 345                 350
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```
aag ctg ggc aaa ttg aat gcc taa                                         1080
Lys Leu Gly Lys Leu Asn Ala
        355                 360


<210> 29
<211> 20
<212> PRT
<213> Homo sapiens

<400> 29
Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
  1               5                  10                  15

Leu Ser Phe His
             20


<210> 30
<211> 63
<212> PRT
<213> Homo sapiens

<400> 30
Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile Tyr Ala Leu Gln Glu
  1               5                  10                  15

Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser Pro Thr Pro Ser Pro
             20                  25                  30

Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val Gln Lys Glu Ile Asp
         35                  40                  45

Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn Ile Pro Gln Leu
     50                  55                  60


<210> 31
<211> 79
<212> PRT
<213> Homo sapiens

<400> 31
Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly Pro Ala Arg Val His
  1               5                  10                  15

Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile Lys Thr Asp Leu Gly
             20                  25                  30

Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu
         35                  40                  45

Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile Met Ser Leu Leu Asn
     50                  55                  60

Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr Ile Thr Ala Ala
 65                  70                  75
```

```
<210> 32
<211> 21
<212> PRT
<213> Homo sapiens

<400> 32
Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val Asn Asp Arg Met Thr
  1               5                  10                  15

Thr Glu Glu Arg Glu
             20


<210> 33
<211> 142
<212> PRT
<213> Homo sapiens

<400> 33
Phe Pro Thr Gly Gln Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp
  1               5                  10                  15

Thr Glu Ser Glu His Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys
             20                  25                  30

Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser
         35                  40                  45

Met Met Ser Thr Ile Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe
     50                  55                  60

Leu Glu Arg Leu Arg Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro
 65                  70                  75                  80

Asp Ser Ser Glu Gly Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln
                 85                  90                  95

Ser Ala Ala Asp Ile Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro
            100                 105                 110

Glu Gln Asn Leu Glu Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr
        115                 120                 125

Asn Arg Asp Gln Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp
    130                 135                 140


<210> 34
<211> 29
<212> PRT
<213> Homo sapiens

<400> 34
Lys Lys Gly His Arg Phe Ser His Asp Pro Gln Ala Ser Gly Leu Trp
  1               5                  10                  15
```

```
Arg Leu Trp Lys Arg Glu Lys Leu Gly Lys Leu Asn Ala
            20                  25


<210> 35
<211> 685
<212> PRT
<213> Homo sapiens

<400> 35
Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
 1               5                  10                  15

Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Xaa Glu Glu Gly
            20                  25                  30

Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
        35                  40                  45

Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
    50                  55                  60

Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
65                  70                  75                  80

Ile His His Thr Xaa Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
                85                  90                  95

Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
            100                 105                 110

Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys Xaa Leu Lys Ser Xaa
        115                 120                 125

Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
    130                 135                 140

Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
145                 150                 155                 160

Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
                165                 170                 175

Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
            180                 185                 190

Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
        195                 200                 205

Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
    210                 215                 220

Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
225                 230                 235                 240

Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
                245                 250                 255
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```
Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
            260                 265                 270

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
        275                 280                 285

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
    290                 295                 300

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
305                 310                 315                     320

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
                325                 330                 335

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
            340                 345                 350

Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
        355                 360                 365

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
    370                 375                 380

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
385                 390                 395                     400

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
                405                 410                 415

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
            420                 425                 430

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
        435                 440                 445

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
    450                 455                 460

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
465                 470                 475                     480

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
                485                 490                 495

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
            500                 505                 510

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
        515                 520                 525

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
    530                 535                 540

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
545                 550                 555                     560
```

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
565 570 575

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
580 585 590

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
595 600 605

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
610 615 620

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
625 630 635 640

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
645 650 655

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser Xaa Ser Gly Arg
660 665 670

Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys Xaa
675 680 685

<210> 36
<211> 360
<212> PRT
<213> Homo sapiens

<400> 36
Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
1 5 10 15

Leu Ser Phe His Xaa Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
20 25 30

Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
35 40 45

Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
50 55 60

Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
65 70 75 80

Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
85 90 95

Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
100 105 110

Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
115 120 125

Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile
130 135 140

Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr
145 150 155 160

Ile Thr Ala Ala Xaa Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val
165 170 175

Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly Gln
180 185 190

Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu His
195 200 205

Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu
210 215 220

Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile
225 230 235 240

Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg
245 250 255

Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly
260 265 270

Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile
275 280 285

Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu
290 295 300

Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu
305 310 315 320

Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg Phe
325 330 335

Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg Glu
340 345 350

Lys Leu Gly Lys Leu Asn Ala Xaa
355 360

<210> 37
<211> 26
<212> ADN
<213> Homo sapiens

<400> 37
ggaccataga ggacactcca ggacta 26

<210> 38
<211> 25
<212> ADN
<213> Homo sapiens

<400> 38
cctcagtcct gctgctggat catct 25

<210> 39
<211> 27
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Val Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala
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Asn Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe
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Gly Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln
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Ile Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile
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Val Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly
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ctgagctttc gctcgccatc caccactgct gtttgccgcc accgcagacc cgccgctgac 420

tcccatccct ctggatcatg cagggtgtcc gctgtgctcc tgatccagcg aggcacccat 480

tgccgctccc aatcgggcta aaggcttgcc attgttcctg catggctaag tgcctgggtt 540

catcctaatt gagctgaaca ctagtcactg ggttccatgg ttctcttctg tgacccacag 600

cttctaatag agctataaca ctcaccgcat ggcccaaggt tccattcctt gaatccataa 660

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Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
1 5 10 15

caa caa gtt ctt aaa aca tta caa gga acc tat ccc tga gaa gag gga 96
Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Glu Glu Gly
20 25 30

aaa gaa cta ttc cac cct tgt gac atg gta tta gtc aag tcc ctt ccc 144
Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
35 40 45

tct aat tcc cca tcc cta gat aca tcc tgg gaa gga ccc tac cca gtc 192
Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
50 55 60

att tta tct acc cca act gcg gtt aaa gtg gct gga gtg gag tct tgg 240

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Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
    65                  70                  75

ata cat cac act tga gtc aaa tcc tgg ata ctg cca aag gaa cct gaa      288
Ile His His Thr     Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
80                      85                  90

aat cca gga gac aac gct agc tat tcc tgt gaa cct cta gag gat ttg      336
Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
95                  100                 105                 110

cgc ctg ctc ttc aaa caa caa cca gga gga aag taa cta aaa tca taa      384
Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys     Leu Lys Ser
                115                 120

atc ccc atg gcc ctc cct tat cat att ttt ctc ttt act gtt ctt tta      432
Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
125                 130                 135                 140

ccc tct ttc act ctc act gca ccc cct cca tgc cgc tgt atg acc agt      480
Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
                145                 150                 155

agc tcc cct tac caa gag ttt cta tgg aga atg cag cgt ccc gga aat      528
Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
            160                 165                 170

att gat gcc cca tcg tat agg agt ctt tct aag gga acc ccc acc ttc      576
Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
        175                 180                 185

act gcc cac acc cat atg ccc cgc aac tgc tat cac tct gcc act ctt      624
Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
    190                 195                 200

tgc atg cat gca aat act cat tat tgg aca gga aaa atg att aat cct      672
Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
205                 210                 215                 220

agt tgt cct gga gga ctt gga gtc act gtc tgt tgg act tac ttc acc      720
Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
                225                 230                 235

caa act ggt atg tct gat ggg ggt gga gtt caa gat cag gca aga gaa      768
Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
            240                 245                 250

aaa cat gta aaa gaa gta atc tcc caa ctc acc cgg gta cat ggc acc      816
Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
        255                 260                 265

tct agc ccc tac aaa gga cta gat ctc tca aaa cta cat gaa acc ctc      864
Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
    270                 275                 280

cgt acc cat act cgc ctg gta agc cta ttt aat acc acc ctc act ggg      912
Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
285                 290                 295                 300

ctc cat gag gtc tcg gcc caa aac cct act aac tgt tgg ata tgc ctc      960
Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
                305                 310                 315
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ccc ctg aac ttc agg cca tat gtt tca atc cct gta cct gaa caa tgg 1008
Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
320 325 330

aac aac ttc agc aca gaa ata aac acc act tcc gtt tta gta gga cct 1056
Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
335 340 345

ctt gtt tcc aat ctg gaa ata acc cat acc tca aac ctc acc tgt gta 1104
Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
350 355 360

aaa ttt agc aat act aca tac aca acc aac tcc caa tgc atc agg tgg 1152
Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
365 370 375 380

gta act cct ccc aca caa ata gtc tgc cta ccc tca gga ata ttt ttt 1200
Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
385 390 395

gtc tgt ggt acc tca gcc tat cgt tgt ttg aat ggc tct tca gaa tct 1248
Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
400 405 410

atg tgc ttc ctc tca ttc tta gtg ccc cct atg acc atc tac act gaa 1296
Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
415 420 425

caa gat tta tac agt tat gtc ata tct aag ccc cgc aac aaa aga gta 1344
Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
430 435 440

ccc att ctt cct ttt gtt ata gga gca gga gtg cta ggt gca cta ggt 1392
Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
445 450 455 460

act ggc att ggc ggt atc aca acc tct act cag ttc tac tac aaa cta 1440
Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
465 470 475

tct caa gaa cta aat ggg gac atg gaa cgg gtc gcc gac tcc ctg gtc 1488
Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
480 485 490

acc ttg caa gat caa ctt aac tcc cta gca gca gta gtc ctt caa aat 1536
Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
495 500 505

cga aga gct tta gac ttg cta acc gct gaa aga ggg gga acc tgt tta 1584
Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
510 515 520

ttt tta ggg gaa gaa tgc tgt tat tat gtt aat caa tcc gga atc gtc 1632
Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
525 530 535 540

act gag aaa gtt aaa gaa att cga gat cga ata caa cgt aga gca gag 1680
Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
545 550 555

gag ctt cga aac act gga ccc tgg ggc ctc ctc agc caa tgg atg ccc 1728
Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro

560 565 570

tgg att ctc ccc ttc tta gga cct cta gca gct ata ata ttg cta ctc 1776
Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
575 580 585

ctc ttt gga ccc tgt atc ttt aac ctc ctt gtt aac ttt gtc tct tcc 1824
Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
590 595 600

aga atc gaa gct gta aaa cta caa atg gag ccc aag atg cag tcc aag 1872
Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
605 610 615 620

act aag atc tac cgc aga ccc ctg gac cgg cct gct agc cca cga tct 1920
Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
625 630 635

gat gtt aat gac atc aaa ggc acc cct cct gag gaa atc tca gct gca 1968
Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
640 645 650

caa cct cta cta cgc ccc aat tca gca gga agc agt tag agc ggt cgt 2016
Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser Ser Gly Arg
655 660 665

cgg cca acc tcc cca aca gca ctt agg ttt tcc tgt tga 2055
Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys
670 675

<210> 23 <211> 28 <212> PRT <213> Homo sapiens <400> 23

Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
1 5 10 15

Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro
20 25

<210> 24 <211> 55 <212> PRT <213> Homo sapiens <400> 24

Glu Glu Gly Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys
1 5 10 15

Ser Leu Pro Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro
20 25 30

Tyr Pro Val Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val
35 40 45

Glu Ser Trp Ile His His Thr
50 55

<210> 25 <211> 38 <212> PRT <213> Homo sapiens <400> 25

Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu Asn Pro Gly Asp Asn

1 5 10 15

Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu Arg Leu Leu Phe Lys
20 25 30

Gln Gln Pro Gly Gly Lys
35

<210> 26 <211> 540 <212> PRT <213> Homo sapiens <400> 26

Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
1 5 10 15

Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
20 25 30

Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
35 40 45

Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
50 55 60

Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
65 70 75 80

Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
85 90 95

Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
100 105 110

Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
115 120 125

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
130 135 140

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
145 150 155 160

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
165 170 175

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
180 185 190

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp

195 200 205

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
210 215 220

Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
225 230 235 240

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
245 250 255

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
260 265 270

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
275 280 285

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
290 295 300

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
305 310 315 320

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
325 330 335

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
340 345 350

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
355 360 365

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
370 375 380

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
385 390 395 400

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
405 410 415

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
420 425 430

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
435 440 445

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
450 455 460

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
465 470 475 480

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
485 490 495

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
500 505 510

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
515 520 525

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser
530 535 540

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1 5 10 15

<210> 28 <211> 1080 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)..(1080)
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Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
1 5 10 15

ctt tct ttt cat taa gag aca act cac aat tat gta aaa agt gtg att 96
Leu Ser Phe His Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
20 25 30

tat gcc cta cag gaa gcc ttc aga gtc tac ctc cct atc cca gca tcc 144
Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
35 40 45

ccg act cct tcc cca act aat aag gac ccc cct tca acc caa atg gtc 192
Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
50 55 60

caa aag gag ata gac aaa agg gta aac agt gaa cca aag agt gcc aat 240
Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
65 70 75

att ccc caa tta tga ccc ctc caa gca gtg gga gga aga gaa ttc ggc 288
Ile Pro Gln Leu Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
80 85 90

cca gcc aga gtg cat gtg cct ttt tct ctc cca gac tta aag caa ata 336
Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
95 100 105 110

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aaa aca gac tta ggt aaa ttc tca gat aac cct gat ggc tat att gat    384
Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
                115                 120                 125

gtt tta caa ggg tta gga caa ttc ttt gat ctg aca tgg aga gat ata    432
Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile
            130                 135                 140

atg tca ctg cta aat cag aca cta acc cca aat gag aga agt gcc acc    480
Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr
        145                 150                 155

ata act gca gcc tga gag ttt ggc gat ctc tgg tat ctc agt cag gtc    528
Ile Thr Ala Ala     Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val
    160                 165                 170

aat gat agg atg aca aca gag gaa aga gaa tga ttc ccc aca ggc cag    576
Asn Asp Arg Met Thr Thr Glu Glu Arg Glu     Phe Pro Thr Gly Gln
    175                 180                 185

cag gca gtt ccc agt cta gac cct cat tgg gac aca gaa tca gaa cat    624
Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu His
    190                 195                 200

gga gat tgg tgc tgc aga cat ttg cta act tgt gtg cta gaa gga cta    672
Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu
205                 210                 215                 220

agg aaa act agg aag aag tct atg aat tac tca atg atg tcc acc ata    720
Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile
                225                 230                 235

aca cag gga agg gaa gaa aat cct act gcc ttt ctg gag aga cta agg    768
Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg
            240                 245                 250

gag gca ttg agg aag cgt gcc tct ctg tca cct gac tct tct gaa ggc    816
Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly
        255                 260                 265

caa cta atc tta aag cgt aag ttt atc act cag tca gct gca gac att    864
Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile
    270                 275                 280

aga aaa aaa ctt caa aag tct gcc gta ggc ccg gag caa aac tta gaa    912
Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu
285                 290                 295                 300

acc cta ttg aac ttg gca acc tcg gtt ttt tat aat aga gat cag gag    960
Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu
                305                 310                 315

gag cag gcg gaa cag gac aaa cgg gat taa aaa aaa ggc cac cgc ttt   1008
Glu Gln Ala Glu Gln Asp Lys Arg Asp     Lys Lys Gly His Arg Phe
            320                 325                     330

agt cat gac cct cag gca agt gga ctt tgg agg ctc tgg aaa agg gaa   1056
Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg Glu
            335                 340                 345

aag ctg ggc aaa ttg aat gcc taa                                   1080
Lys Leu Gly Lys Leu Asn Ala
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350

<210> 29 <211> 20 <212> PRT <213> Homo sapiens <400> 29

Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
1 5 10 15

Leu Ser Phe His
20

<210> 30 <211> 63 <212> PRT <213> Homo sapiens <400> 30

Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile Tyr Ala Leu Gln Glu
1 5 10 15

Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser Pro Thr Pro Ser Pro
20 25 30

Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val Gln Lys Glu Ile Asp
35 40 45

Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn Ile Pro Gln Leu
50 55 60

<210> 31 <211> 79 <212> PRT <213> Homo sapiens <400> 31

Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly Pro Ala Arg Val His
1 5 10 15

Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile Lys Thr Asp Leu Gly
20 25 30

Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu
35 40 45

Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile Met Ser Leu Leu Asn
50 55 60

Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr Ile Thr Ala Ala
65 70 75

<210> 32 <211> 21 <212> PRT <213> Homo sapiens <400> 32

Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val Asn Asp Arg Met Thr
1 5 10 15

Thr Glu Glu Arg Glu
20

<210> 33 <211> 142 <212> PRT <213> Homo sapiens <400> 33

Phe Pro Thr Gly Gln Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp
1   5   10   15

Thr Glu Ser Glu His Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys
            20   25   30

Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser
        35   40   45

Met Met Ser Thr Ile Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe
    50   55   60

Leu Glu Arg Leu Arg Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro
65   70   75   80

Asp Ser Ser Glu Gly Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln
                85   90   95

Ser Ala Ala Asp Ile Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro
            100   105   110

Glu Gln Asn Leu Glu Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr
        115   120   125

Asn Arg Asp Gln Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp
    130   135   140

<210> 34 <211> 29 <212> PRT <213> Homo sapiens <400> 34

Lys Lys Gly His Arg Phe Ser His Asp Pro Gln Ala Ser Gly Leu Trp
1   5   10   15

Arg Leu Trp Lys Arg Glu Lys Leu Gly Lys Leu Asn Ala
            20   25

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Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
1   5   10   15

Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Xaa Glu Glu Gly
            20   25   30

Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
        35   40   45

Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
    50   55   60

Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
65   70   75   80

Ile His His Thr Xaa Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
                85   90   95

Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
            100   105   110

Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys Xaa Leu Lys Ser Xaa
        115   120   125

Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
    130   135   140

Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
145   150   155   160

Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
                165   170   175

Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
            180   185   190

Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
        195   200   205

Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
    210   215   220

Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
225   230   235   240

Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
                245   250   255

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
260 265 270

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
275 280 285

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
290 295 300

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
305 310 315 320

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
325 330 335

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
340 345 350

Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
355 360 365

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
370 375 380

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
385 390 395 400

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
405 410 415

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
420 425 430

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
435 440 445

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
450 455 460

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
465 470 475 480

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
485 490 495

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn

500 505 510

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
515 520 525

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
530 535 540

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
545 550 555 560

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
565 570 575

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
580 585 590

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
595 600 605

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
610 615 620

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
625 630 635 640

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
645 650 655

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser Xaa Ser Gly Arg
660 665 670

Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys Xaa
675 680 685

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Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
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Ser Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met
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Val Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala
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Asn Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe
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Gly Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln
            100                 105                 110

Ile Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile
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Asp Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp
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Thr Ile Thr Ala Ala Xaa Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln
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Val Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly
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Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg
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